ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Insuman Rapid 40 IU/ml solution for injection in a vial
Insuman Rapid 100 IU/ml solution for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insuman Rapid 40 IU/ml in a vial
Each ml contains 40 IU insulin human (equivalent to 1.4 mg).
Each vial contains 10 ml of solution for injection, equivalent to 400 IU insulin.

Insuman Rapid 100 IU/ml in a vial
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of solution for injection, equivalent to 500 IU insulin, or 10 ml of solution for injection, equivalent to 1000 IU insulin.

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin*.

Insuman Rapid is a neutral insulin solution (regular insulin).

*Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required. Insuman Rapid is also suitable for the treatment of hyperglycaemic coma and ketoacidosis, as well as for achieving pre-, intra- and post-operative stabilisation in patients with diabetes mellitus.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insuman Rapid is injected subcutaneously 15 to 20 minutes before a meal.

In the treatment of severe hyperglycaemia or ketoacidosis in particular, insulin administration is part of a complex therapeutic regimen which includes measures to protect patients from possible severe complications of a relatively rapid lowering of blood glucose. This regimen requires close monitoring

(metabolic status, acid-base and electrolyte status, vital parameters etc.) in an intensive care unit or similar setting.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population(≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insuman Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.

Insuman Rapid is administered subcutaneously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Insuman Rapid 40 IU/ml in a vial
Only injection syringes designed for this strength of insulin (40 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insuman Rapid 100 IU/ml in a vial
Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insuman Rapid may also be administered intravenously. Intravenous insulin therapy must generally take place in an intensive care unit or under comparable monitoring and treatment conditions (see "Daily doses and timing of administration").

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients hypersensitive to Insuman Rapid for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insuman Rapid, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insuman Rapid
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished.

The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5)

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insuman formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insuman with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insuman is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies are available. Insulin does not cross the placental barrier. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insuman Rapid can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon

(≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy; Cutaneous amyloidosis
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4.).

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC Code: A10AB01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insuman Rapid is an insulin with rapid onset and short duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1 and 4 hours after injection and the duration of action is 7 to 9 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic

effects was found. Local tolerability studies following subcutaneous and intramuscular administration in rabbits gave no remarkable findings. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insuman Rapid must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insuman Rapid must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insuman Rapid must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insuman Rapid next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Insuman Rapid 40 IU/ml in a vial
10 ml solution in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl

rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

Insuman Rapid 100 IU/ml in a vial
5 ml solution in a vial and 10 ml solution in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Do not shake the vial vigorously as this may cause frothing. Froth may interfere with the correct measurement of the dose.

Insuman Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

Insuman Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.

It must be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Rapid may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/028
EU/1/97/030/029
EU/1/97/030/031
EU/1/97/030/032
EU/1/97/030/196
EU/1/97/030/197

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 1997
Date of latest renewal: 21 February 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insuman Rapid 100 IU/ml solution for injection in a cartridge
Insuman Rapid SoloStar 100 IU/ml solution for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insuman Rapid 100 IU/ml in a cartridge
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge contains 3 ml of solution for injection, equivalent to 300 IU insulin.

Insuman Rapid 100 IU/ml in a pre-filled pen
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each pen contains 3 ml of solution for injection, equivalent to 300 IU insulin.

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin*.

Insuman Rapid is a neutral insulin solution (regular insulin).

*Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insuman Rapid is injected subcutaneously 15 to 20 minutes before a meal.

Insuman Rapid 100 IU/ml in a pre-filled pen
SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if

- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations

Elderly population(≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insuman Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.

Insuman Rapid is administered subcutaneously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Insuman Rapid 100 IU/ml in a cartridge
Insuman Rapid 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe or intravenous injection is necessary, a vial should be used (see section 4.4).

Insuman Rapid SoloStar 100 IU/ml in a pre-filled pen
Insuman Rapid SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe or intravenous injection is necessary, a vial should be used (see section 4.4). Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients hypersensitive to Insuman Rapid for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insuman Rapid, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insuman Rapid
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:

- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Intercurrent illness

Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insuman Rapid 100 IU/ml in a cartridge

Pens to be used with Insuman Rapid 100 IU/ml in cartridges

Insuman Rapid 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe or intravenous injection is necessary, a vial should be used.
The Insuman Rapid cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insuman Rapid in 0.5 unit dose increments
- ClikSTAR, Tactipen, Autopen 24, AllStar and AllStar PRO which all deliver Insuman Rapid in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens (see section 4.2 and 6.6).
Not all of these pens may be marketed in your country.

Insuman Rapid SoloStar 100 IU/ml in a pre-filled pen

Handling of the pen

Insuman Rapid SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe or intravenous injection is necessary, a vial should be used (see section 4.2).Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors

Medication errors have been reported in which other Insuman formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insuman with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insuman is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.
Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies are available. Insulin does not cross the placental barrier. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insuman Rapid can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions

The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy; Cutaneous amyloidosis
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC Code: A10AB01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insuman Rapid is an insulin with rapid onset and short duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1 and 4 hours after injection and the duration of action is 7 to 9 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Local tolerability studies following subcutaneous and intramuscular administration in rabbits gave no remarkable findings. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insuman Rapid must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insuman Rapid 100 IU/ml in a cartridge or Insuman rapid SoloStar 100 IU/ml in a pre-filled pen must not be mixed with any other insulin or with insulin analogues.
Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution.

6.3 Shelf life

2 years.

Shelf life after first use
Insuman Rapid 100 IU/ml in a cartridge
The cartridge in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

Insuman rapid SoloStar 100 IU/ml in a pre-filled pen
The pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Insuman Rapid 100 IU/ml in a cartridge

Unopened cartridges
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insuman Rapid next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
For storage conditions after first opening of the medicinal product, see section 6.3.

Insuman rapid SoloStar 100 IU/ml in a pre-filled pen
Not in-use pens
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insuman Rapid next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Insuman Rapid 100 IU/ml in a cartridge
3 ml solution in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Not all pack sizes may be marketed.

Insuman rapid SoloStar 100 IU/ml in a pre-filled pen
3 ml solution in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insuman Rapid 100 IU/ml in a cartridge
Insulin pen
Insuman Rapid 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe or intravenous injection is necessary, a vial should be used. The Insuman Rapid cartridges are to be used only in conjunction with the pens: ClikSTAR, Autopen 24, Tactipen, AllStar, AllStar PRO or JuniorSTAR (see section 4.2 and 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

Cartridges
Before insertion into the pen, Insuman Rapid must be kept at room temperature for 1 to 2 hours. Inspect the cartridge before use. Insuman Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insuman Rapid must not be used in external or implanted insulin pumps or in peristaltic pumps with silicone tubing.

It must be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Rapid cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman rapid SoloStar 100 IU/ml in a pre-filled pen
Insuman Rapid SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe or intravenous injection is necessary, a vial should be used (see section 4.2 and 4.4).

Insuman Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

Empty pens must never be re-used and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Before using the SoloStar pre-filled pen, the Instructions for Use included in the package leaflet must be read carefully.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/030
EU/1/97/030/055
EU/1/97/030/056
EU/1/97/030/085

EU/1/97/030/090
EU/1/97/030/095
EU/1/97/030/140
EU/1/97/030/141
EU/1/97/030/142
EU/1/97/030/143
EU/1/97/030/144
EU/1/97/030/145

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 1997
Date of latest renewal: 21 February 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insuman Basal 40 IU/ml suspension for injection in a vial
Insuman Basal 100 IU/ml suspension for injection in a vial
Insuman Basal 100 IU/ml suspension for injection in a cartridge
Insuman Basal SoloStar 100 IU/ml suspension for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insuman Basal 40 IU/ml in a vial
Each ml contains 40 IU insulin human (equivalent to 1.4 mg).
Each vial contains 10 ml of suspension for injection, equivalent to 400 IU insulin.

Insuman Basal 100 IU/ml in a vial
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of suspension for injection, equivalent to 500 IU insulin, or 10 ml of suspension for injection, equivalent to 1000 IU insulin.

Insuman Basal 100 IU/ml in a cartridge, Insuman Basal SoloStar 100 IU/ml in a pre-filled pen
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge or pen contains 3 ml of suspension for injection, equivalent to 300 IU insulin.

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin*.

Insuman Basal is an isophane insulin suspension.

*Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insuman Basal is injected subcutaneously 45 to 60 minutes before a meal.

Insuman Basal SoloStar 100 IU/ml in a pre-filled pen
SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insuman Basal must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Insuman Basal is administered subcutaneously. Insuman Basal must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Insuman Basal 40 IU/ml in a vial
Only injection syringes designed for this strength of insulin (40 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insuman Basal 100 IU/ml in a vial
Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insuman Basal 100 IU/ml in a cartridge
Insuman Basal 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used (see section 4.4).

Insuman Basal SoloStar100 IU/ml in a pre-filled pen
Insuman Basal SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.4).
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients hypersensitive to Insuman Basal for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insuman Basal, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insuman Basal
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,

- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Intercurrent illness

Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insuman Basal 100 IU/ml in a cartridge

Pens to be used with Insuman Basal 100 IU/ml in cartridges

Insuman Basal 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used.
The Insuman Basal cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insuman Basal in 0.5 unit dose increments
- ClikSTAR, Tactipen, Autopen 24, and AllStar and AllStar PRO which all deliver Insuman Basal in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.
Not all of these pens may be marketed in your country (see section 4.2 and 6.6).

Insuman Basal SoloStar100 IU/ml in a pre-filled pen

Handling of the pen

Insuman Basal SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2).
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors

Medication errors have been reported in which other Insuman formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insuman with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insuman is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies are available. Insulin does not cross the placental barrier. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insuman Basal can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of

hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions

The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy; Cutaneous amyloidosis
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting, ATC Code: A10AC01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,

- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insuman Basal (an isophane insulin suspension) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 60 minutes, the phase of maximum action is between 3 and 4 hours after injection and the duration of action is 11 to 20 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
Insuman Basal must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insuman Basal 40 IU/ml in a vial, Insuman Basal 100 IU/ml in a vial
Insuman Basal must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insuman Basal must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

Insuman Basal 100 IU/ml in a cartridge
Insuman Basal 100 IU/ml in cartridges must not be mixed with any other insulin or with insulin analogues (see section 4.2, 4.4 and 6.6).

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

Insuman Basal SoloStar 100 IU/ml in a pre-filled pen
Insuman Basal SoloStar 100 IU/ml in a pre-filled pen must not be mixed with any other insulin or with

insulin analogues (see section 4.2, 4.4 and 6.6).

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

Shelf life after first use of the cartridge, pen
The cartridge in-use (in the insulin pen) or carried as a spare, the pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge or pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened vials, unopened cartridges, not in-use pens
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insuman Basal next to the freezer compartment or a freezer pack.
Keep the vial, cartridge or pre-filled pen in the outer carton in order to protect from light.

Opened vials, in-use cartridges, in-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Insuman Basal 40 IU/ml in a vial
10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

Insuman Basal 100 IU/ml in a vial
5 ml suspension in a vial and 10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

Insuman Basal 100 IU/ml in a cartridge, Insuman Basal SoloStar 100 IU/ml in a pre-filled pen
3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).

Pre-filled pen
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.

Pack size
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insuman Basal 40 IU/ml in a vial, Insuman Basal 100 IU/ml in a vial
Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insuman Basal must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insuman Basal must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that insulin protamine crystals dissolve in an acid pH range.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Basal may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman Basal 100 IU/ml in a cartridge
Insulin pen
Insuman Basal 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used. The Insuman Basal cartridges are to be used only in conjunction with the pens: ClikSTAR, Autopen 24, Tactipen, AllStar , AllStar PRO or JuniorSTAR (see section 4.2 and 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer’s instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

Cartridges
Before insertion into the pen, Insuman Basal must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the pen, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the pen back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insuman Basal must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new cartridge yielding a uniform suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insuman Basal must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that insulin protamine crystals dissolve in an acid pH range.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Basal cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman Basal SoloStar 100 IU/ml in a pre-filled pen
Insuman Basal SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2 and 4.4).

Before first use, Insuman Basal must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the pen back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents. Later on, the insulin must be resuspended again prior to each injection.

After resuspension, the fluid must have a uniformly milky appearance. Insuman Basal must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new pen yielding a uniform suspension must be used. It is also necessary to change to a new pen if the insulin requirement changes substantially.

Empty pens must never be re-used and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that insulin protamine crystals dissolve in an acid pH range.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Before using the SoloStar pre-filled pen, the Instructions for Use included in the package leaflet must be read carefully.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/033
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EU/1/97/030/058
EU/1/97/030/086
EU/1/97/030/091
EU/1/97/030/096
EU/1/97/030/146
EU/1/97/030/147
EU/1/97/030/148
EU/1/97/030/149
EU/1/97/030/150
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 1997
Date of latest renewal: 21 February 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 15 100 IU/ml suspension for injection in a vial
Insuman Comb 15 100 IU/ml suspension for injection in a cartridge
Insuman Comb 15 SoloStar 100 IU/ml suspension for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insuman Comb 15 100 IU/ml in a vial
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of suspension for injection, equivalent to 500 IU insulin.

Insuman Comb 15 100 IU/ml in a cartridge, Insuman Comb 15 SoloStar 100 IU/ml in a pre-filled pen
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge or pen contains 3 ml of suspension for injection, equivalent to 300 IU insulin.

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin*.

Insuman Comb 15 is a biphasic isophane insulin suspension consisting of 15% dissolved insulin and 85% crystalline protamine insulin.

* Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insuman Comb 15 is injected subcutaneously 30 to 45 minutes before a meal.

Insuman Comb 15 SoloStar 100 IU/ml in a pre-filled pen
SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insuman Comb 15 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Insuman Comb 15 is administered subcutaneously. Insuman Comb 15 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Insuman Comb 15 100 IU/ml in a vial
Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insuman Comb 15 100 IU/ml in a cartridge
Insuman Com 15 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used (see section 4.4).

Insuman Comb 15 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 15 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.4).
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients hypersensitive to Insuman Comb 15 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.
In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insuman Comb 15, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insuman Comb 15
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the

patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:

- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insuman Comb 15 100 IU/ml in a cartridge
Pens to be used with Insuman Comb 15 100 IU/ml in cartridges
Insuman Comb 15 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used.
The Insuman Com 15 cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insuman Comb 15 in 0.5 unit dose increments
- ClikSTAR, Tactipen, Autopen 24, AllStar and AllStar PRO which all deliver Insuman Comb 15 in 1 unit dose increments.
These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.
Not all of these pens may be marketed in your country (see section 4.2 and 6.6).

Insuman Comb 15 SoloStar 100 IU/ml in a pre-filled pen
Handling of the pen
Insuman Comb 15 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2).
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors
Medication errors have been reported in which other Insuman formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insuman with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insuman is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies are available. Insulin does not cross the placental barrier. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insuman Comb 15 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed

use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions

The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy; Cutaneous amyloidosis
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions

Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insuman Comb 15 (a biphasic isophane insulin suspension with 15% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 11 to 20 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insuman Comb 15 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insuman Comb 15 100 IU/ml in a vial
Insuman Comb 15 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insuman Comb 15 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

Insuman Comb 15 100 IU/ml in a cartridge
Insuman Comb 15 100 IU/ml in cartridges must not be mixed with any other insulin or with insulin analogues (see section 4.2, 4.4 and 6.6).

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

Insuman Comb 15 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 15 SoloStar 100 IU/ml in a pre-filled pen must not be mixed with any other insulin or with insulin analogues (see section 4.2, 4.4 and 6.6).

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.

Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

Shelf life after first use of the cartridge, pen
The cartridge in-use (in the insulin pen) or carried as a spare, the pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge or pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened vials, unopened cartridges, not in-use pens
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insuman Comb 15 next to the freezer compartment or a freezer pack.
Keep the vial, cartridge or pre-filled pen in the outer carton in order to protect from light.

Opened vials, in-use cartridges, in-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Insuman Comb 15 100 IU/ml in a vial
5 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

Insuman Comb 15 100 IU/ml in a cartridge, Insuman Comb 15 SoloStar 100 IU/ml in a pre-filled pen
3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).

Pre-filled pen
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.

Pack size
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insuman Comb 15 100 IU/ml in a vial
Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted

appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 15 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insuman Comb 15 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Comb 15 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman Comb 15 100 IU/ml in a cartridge
Insulin pen
Insuman Comb 15 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used. The Insuman Comb 15 cartridges are to be used only in conjunction with the pens: ClikSTAR, Autopen 24, Tactipen, AllStar, AllStar PRO or JuniorSTAR (see section 4.2 and 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

Cartridges
Before insertion into the pen, Insuman Comb 15 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the pen, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the pen back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 15 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new cartridge yielding a uniform

suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insuman Comb 15 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Comb 15 cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman Comb 15 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 15 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2 and 4.4).

Before first use, Insuman Comb 15 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the pen back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents. Later on, the insulin must be resuspended again prior to each injection.

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 15 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new pen yielding a uniform suspension must be used. It is also necessary to change to a new pen if the insulin requirement changes substantially.

Empty pens must never be re-used and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Before using the SoloStar pre-filled pen, the Instructions for Use included in the package leaflet must be read carefully.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/038
EU/1/97/030/039
EU/1/97/030/040
EU/1/97/030/059
EU/1/97/030/060
EU/1/97/030/087
EU/1/97/030/092
EU/1/97/030/097
EU/1/97/030/152
EU/1/97/030/153
EU/1/97/030/154
EU/1/97/030/155
EU/1/97/030/156
EU/1/97/030/157

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 1997
Date of latest renewal: 21 February 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 25 40 IU/ml suspension for injection in a vial
Insuman Comb 25 100 IU/ml suspension for injection in a vial
Insuman Comb 25 100 IU/ml suspension for injection in a cartridge
Insuman Comb 25 SoloStar 100 IU/ml suspension for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insuman Comb 25 40 IU/ml in a vial
Each ml contains 40 IU insulin human (equivalent to 1.4 mg).
Each vial contains 10 ml of suspension for injection, equivalent to 400 IU insulin.

Insuman Comb 25 100 IU/ml in a vial
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of suspension for injection, equivalent to 500 IU insulin.

Insuman Comb 25 100 IU/ml in a cartridge, Insuman Comb 25 SoloStar 100 IU/ml in a pre-filled pen
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge or pen contains 3 ml of suspension for injection, equivalent to 300 IU insulin.

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin*.

Insuman Comb 25 is a biphasic isophane insulin suspension consisting of 25% dissolved insulin and 75% crystalline protamine insulin.

* Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insuman Comb 25 is injected subcutaneously 30 to 45 minutes before a meal.

Insuman Comb 25 SoloStar 100 IU/ml in a pre-filled pen
SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insuman Comb 25 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Insuman Comb 25 is administered subcutaneously. Insuman Comb 25 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Insuman Comb 25 40 IU/ml in a vial
Only injection syringes designed for this strength of insulin (40 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insuman Comb 25 100 IU/ml in a vial
Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insuman Comb 25 100 IU/ml in a cartridge
Insuman Comb 25 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used (see section 4.4).

Insuman Comb 25 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 25 SoloStar100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.4).
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients hypersensitive to Insuman Comb 25 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insuman Comb 25, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insuman Comb 25
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Intercurrent illness

Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insuman Comb 25 100 IU/ml in a cartridge

Pens to be used with Insuman Comb 25 100 IU/ml in cartridges

Insuman Comb 25 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used.
The Insuman Comb 25 cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insuman Comb 25 in 0.5 unit dose increments
- ClikSTAR, Tactipen, Autopen 24, AllStar and AllStar PRO which all deliver Insuman Comb 25 in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.
Not all of these pens may be marketed in your country (see section 4.2 and 6.6).

Insuman Comb 25 SoloStar 100 IU/ml in a pre-filled pen

Handling of the pen

Insuman Comb 25 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2).
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors
Medication errors have been reported in which other Insuman formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insuman with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insuman is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies are available. Insulin does not cross the placental barrier. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insuman Comb 25 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions

The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy; Cutaneous amyloidosis
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insuman Comb 25 (a biphasic isophane insulin suspension with 25% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 12 to 19 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insuman Comb 25 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insuman Comb 25 40 IU/ml in a vial, Insuman Comb 25 100 IU/ml in a vial
Insuman Comb 25 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insuman Comb 25 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

Insuman Comb 25 100 IU/ml in a cartridge
Insuman Comb 25 100 IU/ml in cartridges must also not be mixed with insulins of animal origin or with insulin analogues (see section 4.2, 4.4 and 6.6).

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

Insuman Comb 25 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 25 SoloStar 100 IU/ml in a pre-filled pen must also not be mixed with insulins of animal origin or with insulin analogues (see section 4.2, 4.4 and 6.6).

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

Shelf life after first use of the cartridge, pen
The cartridge in-use (in the insulin pen) or carried as a spare, the pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge or pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened vials, unopened cartridges, not in-use pens
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insuman Comb 25 next to the freezer compartment or a freezer pack.
Keep the vial, cartridge or pre-filled pen in the outer carton in order to protect from light.

Opened vials, in-use cartridges, in-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Insuman Comb 25 40 IU/ml in a vial
10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

Insuman Comb 25 100 IU/ml in a vial
5 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

Insuman Comb 25 100 IU/ml in a cartridge, Insuman Comb 25 SoloStar100 IU/ml in a pre-filled pen
3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).

Pre-filled pen
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.

Pack size
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insuman Comb 25 40 IU/ml in a vial, Insuman Comb 25 100 IU/ml in a vial
Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 25 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insuman Comb 25 must not be administered intravenously and must not be used in infusion pumps or external implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Comb 25 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman Comb 25 100 IU/ml in a cartridge

Insulin pen

Insuman Comb 25 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used.

The Insuman Comb 25 cartridges are to be used only in conjunction with the pens: ClikSTAR, Autopen 24, Tactipen, AllStar, AllStar PRO or JuniorSTAR (see section 4.2 and 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

Cartridges

Before insertion into the pen, Insuman Comb 25 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the pen, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the pen back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 25 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new cartridge yielding a uniform suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insuman Comb 25 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins

Insuman Comb 25 cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman Comb 25 SoloStar 100 IU/ml in a pre-filled pen

Insuman Comb 25 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2 and 4.4).

Before first use, Insuman Comb 25 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the pen back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents. Later on, the insulin must be resuspended again prior to each injection.

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 25 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new pen yielding a uniform suspension must be used. It is also necessary to change to a new pen if the insulin requirement changes substantially.

Empty pens must never be re-used and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Before using the SoloStar pre-filled pen, the Instructions for Use included in the package leaflet must be read carefully.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/043
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EU/1/97/030/062
EU/1/97/030/088
EU/1/97/030/093
EU/1/97/030/098
EU/1/97/030/158
EU/1/97/030/159
EU/1/97/030/160
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 1997
Date of latest renewal: 21 February 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 30 100 IU/ml suspension for injection in a vial
Insuman Comb 30 100 IU/ml suspension for injection in a cartridge
Insuman Comb 30 SoloStar 100 IU/ml suspension for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insuman Comb 30 100 IU/ml in a vial
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of suspension for injection, equivalent to 500 IU insulin, or 10 ml of suspension for injection, equivalent to 1000 IU insulin.

Insuman Comb 30 100 IU/ml in a cartridge, Insuman Comb 30 SoloStar 100 IU/ml in a pre-filled pen
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge or pen contains 3 ml of suspension for injection, equivalent to 300 IU insulin.

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin*.

Insuman Comb 30 is a biphasic isophane insulin suspension consisting of 30% dissolved insulin and 70% crystalline protamine insulin.

* Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insuman Comb 30 is injected subcutaneously 30 to 45 minutes before a meal.

Insuman Comb 30 SoloStar 100 IU/ml in a pre-filled pen
SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insuman Comb 30 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Insuman Comb 30 is administered subcutaneously. Insuman Comb 30 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Insuman Comb 30 100 IU/ml in a vial
Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insuman Comb 30 100 IU/ml in a cartridge
Insuman Comb 30 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used (see section 4.4).

Insuman Comb 30 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 30 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.4).
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients hypersensitive to Insuman Comb 30 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insuman Comb 30, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insuman Comb 30

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting,etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who

- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:

- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the

patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:

- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Intercurrent illness

Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insuman Comb 30 100 IU/ml in a cartridge

Pens to be used with Insuman Comb 30 100 IU/ml in cartridges

Insuman Comb 30 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used.

The Insuman Comb 30 cartridges should only be used with the following pens:

- JuniorSTAR which delivers Insuman Comb 30 in 0.5 unit dose increments
- ClikSTAR, Tactipen, Autopen 24, AllStar and AllStar PRO which all deliver Insuman Comb 30 in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

Not all of these pens may be marketed in your country(see section 4.2 and 6.6).

Insuman Comb 30 SoloStar 100 IU/ml in a pre-filled pen

Handling of the pen

Insuman Comb 30 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2).

Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors

Medication errors have been reported in which other Insuman formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insuman with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insuman is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies are available. Insulin does not cross the placental barrier. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insuman Comb 30 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the

insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy; Cutaneous amyloidosis
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage.
Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insuman Comb 30 (a biphasic isophane insulin suspension with 30% dissolved insulin) is an insulin with gradual onset and long duration of action. Following subcutaneous injection, onset of action is within 30 to 60 minutes, the phase of maximum action is between 2 and 4 hours after injection and the duration of action is 12 to 19 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin

do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insuman Comb 30 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insuman Comb 30 100 IU/ml in a vial
Insuman Comb 30 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insuman Comb 30 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

Insuman Comb 30 100 IU/ml in a cartridge
Insuman Comb 30 100 IU/ml in cartridges must also not be mixed with insulins of animal origin or with insulin analogues (see section 4.2, 4.4 and 6.6).

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

Insuman Comb 30 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 30 SoloStar 100 IU/ml in a pre-filled pen must also not be mixed with insulins of animal origin or with insulin analogues (see section 4.2, 4.4 and 6.6).

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or

direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

Shelf life after first use of the cartridge, pen
The cartridge in-use (in the insulin pen) or carried as a spare, the pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.

The pen containing a cartridge or pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened vials, unopened cartridges, not in-use pens
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insuman Comb 30 next to the freezer compartment or a freezer pack.
Keep the vial, cartridge or pre-filled pen in the outer carton in order to protect from light.

Opened vials, in-use cartridges, in-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Insuman Comb 30 100 IU/ml in a vial
5 ml suspension in a vial and 10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

Insuman Comb 30 100 IU/ml in a cartridge, Insuman Comb 30 SoloStar 100 IU/ml in a pre-filled pen
3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).

Pre-filled pen
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.

Pack size
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insuman Comb 30 100 IU/ml in a vial
Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 30 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes

give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insuman Comb 30 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Comb 30 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman Comb 30 100 IU/ml in a cartridge
Insulin pen
Insuman Comb 30 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used. The Insuman Comb 30 cartridges are to be used only in conjunction with the pens: ClikSTAR, Autopen 24, Tactipen, AllStar , AllStar PRO or JuniorSTAR (see section 4.2 and 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

Cartridges
Before insertion into the pen, Insuman Comb 30 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the pen, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the pen back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 30 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new cartridge yielding a uniform suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insuman Comb 30 must not be administered intravenously and must not be used in infusion pumps or

external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Comb 30 cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman Comb 30 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 30 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2 and 4.4).

Before first use, Insuman Comb 30 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the pen back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents. Later on, the insulin must be resuspended again prior to each injection.

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 30 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new pen yielding a uniform suspension must be used. It is also necessary to change to a new pen if the insulin requirement changes substantially.

Empty pens must never be re-used and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Before using the SoloStar pre-filled pen, the Instructions for Use included in the package leaflet must be read carefully.

Before using the SoloStar pre-filled pen, the Instructions for Use included in the package leaflet must be read carefully.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 1997
Date of latest renewal: 21 February 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 50 40 IU/ml suspension for injection in a vial
Insuman Comb 50 100 IU/ml suspension for injection in a vial
Insuman Comb 50 100 IU/ml suspension for injection in a cartridge
Insuman Comb 50 SoloStar 100 IU/ml suspension for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insuman Comb 50 40 IU/ml in a vial
Each ml contains 40 IU insulin human (equivalent to 1.4 mg).
Each vial contains 10 ml of suspension for injection, equivalent to 400 IU insulin.

Insuman Comb 50 100 IU/ml in a vial
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 5 ml of suspension for injection, equivalent to 500 IU insulin.

Insuman Comb 50 100 IU/ml in a cartridge, Insuman Comb 50 SoloStar 100 IU/ml in a pre-filled pen
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each cartridge or pen contains 3 ml of suspension for injection, equivalent to 300 IU insulin.

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin*.

Insuman Comb 50 is a biphasic isophane insulin suspension consisting of 50% dissolved insulin and 50% crystalline protamine insulin.

* Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

After resuspension, milky-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
The desired blood glucose levels, the insulin preparations to be used and the insulin dose regimen (doses and timings) must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total daily requirement. Insuman Comb 50 is injected subcutaneously 20 to 30 minutes before a meal.

Insuman Comb 50 SoloStar 100 IU/ml in a pre-filled pen
SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insuman Comb 50 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

Insuman Comb 50 is administered subcutaneously. Insuman Comb 50 must never be injected intravenously.

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). Injection sites within an injection area must be rotated from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Insuman Comb 50 40 IU/ml in a vial
Only injection syringes designed for this strength of insulin (40 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insuman Comb 50 100 IU/ml in a vial
Only injection syringes designed for this strength of insulin (100 IU per ml) are to be used. The injection syringes must not contain any other medicinal product or residue (e.g. traces of heparin).

Insuman Comb 50 100 IU/ml in a cartridge
Insuman Comb 50 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used (see section 4.4).

Insuman Comb 50 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 50 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.4).
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients hypersensitive to Insuman Comb 50 for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insuman Comb 50, since they may experience immunological cross-reactions.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insuman Comb 50
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Intercurrent illness

Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insuman Comb 50 100 IU/ml in a cartridge

Pens to be used with Insuman Comb 50 100 IU/ml in cartridges

Insuman Comb 50 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used.
The Insuman Comb 50 cartridges should only be used with the following pens:
- JuniorSTAR which delivers Insuman Comb 50 in 0.5 unit dose increments
- ClikSTAR, Tactipen, Autopen 24, AllStar and AllStar PRO which all deliver Insuman Comb 50 in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.
Not all of these pens may be marketed in your country (see section 4.2 and 6.6).

Insuman Comb 50 SoloStar 100 IU/ml in a pre-filled pen

Handling of the pen

Insuman Comb 50 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2).
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

Medication errors
Medication errors have been reported in which other Insuman formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insuman with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insuman is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies are available. Insulin does not cross the placental barrier. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insuman Comb 50 can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy; Cutaneous amyloidosis
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, intermediate-acting combined with fast-acting, ATC Code: A10AD01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insuman Comb 50 (a biphasic isophane insulin suspension with 50% dissolved insulin) is an insulin with rapid onset and moderately long duration of action. Following subcutaneous injection, onset of action is within 30 minutes, the phase of maximum action is between 1.5 and 4 hours after injection and the duration of action is 12 to 16 hours.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Protamine sulphate,
metacresol,
phenol,
zinc chloride,
sodium dihydrogen phosphate dihydrate,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insuman Comb 50 must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insuman Comb 50 40 IU/ml in a vial, Insuman Comb 50 100 IU/ml in a vial
Insuman Comb 50 must not be mixed with insulin human formulations designed specifically for use in insulin pumps.
Insuman Comb 50 must also not be mixed with insulins of animal origin or with insulin analogues.
Insulins of different concentration (e.g. 100 IU per ml and 40 IU per ml) must not be mixed.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

Insuman Comb 50 100 IU/ml in a cartridge
Insuman Comb 50 100 IU/ml in cartridges must not be mixed with insulins of animal origin or with insulin analogues (see section 4.2, 4.4 and 6.6).

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

Insuman Comb 50 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 50 SoloStar 100 IU/ml in a pre-filled pen must not be mixed with insulins of animal origin or with insulin analogues(see section 4.2, 4.4 and 6.6).

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin suspension.

6.3 Shelf life

2 years.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

Shelf life after first use of the cartridge, pen
The cartridge in-use (in the insulin pen) or carried as a spare, the pen in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
The pen containing a cartridge or pens in-use must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened vials, unopened cartridges, not in-use pens
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insuman Comb 50 next to the freezer compartment or a freezer pack.
Keep the vial, cartridge or pre-filled pen in the outer carton in order to protect from light.

Opened vials, in-use cartridges, in-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Insuman Comb 50 40 IU/ml in a vial
10 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).

Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

Insuman Comb 50 100 IU/ml in a vial
5 ml suspension in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).

Packs of 1 and 5 vials are available.
Not all pack sizes may be marketed.

Insuman Comb 50 100 IU/ml in a cartridge, Insuman Comb 50 SoloStar 100 IU/ml in a pre-filled pen
3 ml suspension in a cartridge (type 1 colourless glass) with a plunger (bromobutyl rubber (type 1)) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl

rubber (type 1)).
Each cartridge contains 3 balls (stainless steel).

Pre-filled pen
The cartridges are sealed in a disposable pen injector.
Injection needles are not included in the pack.

Pack size
Packs of 3, 4, 5, 6, 9 or 10 cartridges are available.
Packs of 3, 4, 5, 6, 9 or 10 pens are available.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Insuman Comb 50 40 IU/ml in a vial, Insuman Comb 50 100 IU/ml in a vial
Before withdrawing insulin from the vial for the first time, remove the plastic protective cap.

Immediately before withdrawal from the vial into the injection syringe, the insulin must be resuspended. This is best done by rolling the vial at an oblique angle between the palms of the hands. Do not shake the vial vigorously as this may lead to changes in the suspension (giving the vial a frosted appearance; see below) and cause frothing. Froth may interfere with the correct measurement of the dose.

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 50 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the vial. These changes sometimes give the vial a frosted appearance. In such cases, a new vial yielding a uniform suspension must be used. It is also necessary to change to a new vial if the insulin requirement changes substantially.

Insuman Comb 50 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Comb 50 may be mixed with all insulin human formulations, but not with those designed specifically for use in insulin pumps. Concerning incompatibility with other insulins, see section 6.2.

If two different insulins have to be drawn into one single injection syringe, it is recommended that the shorter-acting insulin be drawn first to prevent contamination of the vial by the longer-acting preparation. It is advisable to inject immediately after mixing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman Comb 50 100 IU/ml in a cartridge
Insulin pen
Insuman Comb 50 100 IU/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe is necessary, a vial should be used. The Insuman comb 50 cartridges are to be used only in conjunction with the pens: ClikSTAR, Autopen 24, Tactipen, AllStar, AllStar PRO or JuniorSTAR (see section 4.2 and 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

Cartridges
Before insertion into the pen, Insuman Comb 50 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the cartridge back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents.

Later on, when the cartridge has been inserted into the pen, the insulin must be resuspended again prior to each injection. This is best done by gently tilting the pen back and forth (at least ten times).

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 50 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new cartridge yielding a uniform suspension must be used. It is also necessary to change to a new cartridge if the insulin requirement changes substantially.

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

Insuman Comb 50 must not be administered intravenously and must not be used in infusion pumps or external or implanted insulin pumps.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Mixing of insulins
Insuman Comb 50 cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Insuman Comb 50 SoloStar 100 IU/ml in a pre-filled pen
Insuman Comb 50 SoloStar 100 IU/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2 and 4.4).

Before first use, Insuman Comb 50 must be kept at room temperature for 1 to 2 hours and then resuspended to check the contents. This is best done by gently tilting the pen back and forth (at least ten times). Each cartridge contains three small metal balls to facilitate quick and thorough mixing of the contents. Later on, the insulin must be resuspended again prior to each injection.

After resuspension, the fluid must have a uniformly milky appearance. Insuman Comb 50 must not be used if this cannot be achieved, i.e. if the suspension remains clear, for example, or if clumps, particles or flocculation appear in the insulin or stick to the wall or bottom of the cartridge. These changes sometimes give the cartridge a frosted appearance. In such cases, a new pen yielding a uniform suspension must be used. It is also necessary to change to a new pen if the insulin requirement changes substantially.

Empty pens must never be re-used and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only.

It must be remembered that
- insulin protamine crystals dissolve in an acid pH range,
- the soluble insulin part precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Before using the SoloStar pre-filled pen, the Instructions for Use included in the package leaflet must be read carefully.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/048
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10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insuman Infusat 100 IU/ml solution for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Insuman Infusat 100 IU/ml in a vial
Each ml contains 100 IU insulin human (equivalent to 3.5 mg).
Each vial contains 10 ml of solution for injection, equivalent to 1000 IU insulin.

One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin*.

Insuman Infusat is a neutral insulin solution (regular insulin).

* Human insulin is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection .

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diabetes mellitus where treatment with insulin is required.

4.2 Posology and method of administration

Posology
Insuman Infusat has been specially designed for use in external portable insulin pumps. It is specially stabilised to minimise loss of efficacy which may result from mechanical and thermal stress in such pumps. Insuman Infusat is therefore also suitable for continuous insulin infusion with other, conventional injection syringe pumps.

The desired blood glucose levels and the insulin dose regimen must be determined individually and adjusted to suit the patient's diet, physical activity and life-style.

Daily doses and timing of administration
When used in external portable insulin pumps, part of the daily insulin dose is infused continuously ("basal rate"), and the rest is administered in the form of bolus injections before meals. Refer to the operating instructions for detailed information about the infusion pump, its functions and the necessary safety precautions.

There are no fixed rules for insulin dose regimen. However, the average insulin requirement is often 0.5 to 1.0 IU per kg body weight per day. The basal metabolic requirement is 40% to 60% of the total

daily requirement. Consequently, about 40% to 60% of the daily dose is administered at a basal rate, and the rest is given as bolus injections before meals.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≧65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Method of administration
Insuman Infusat must not be used in peristaltic pumps with silicone tubing. Refer to the technical manual for contraindications relating to the use of insulin pumps.

Insuman Infusat may be infused by the subcutaneous route.
Insuman Infusat in a vial may also be used in other insulin pumps for which it has been shown that they are suitable for this insulin (see pump manual).
Only tetrafluoroethylene or polyethylene catheters must be used.

Insulin must always be infused under aseptic conditions. This is facilitated by the special equipment available for the insulin pumps (e.g. catheters, cannulas).

Insulin absorption and hence the blood-glucose-lowering effect of a dose may vary from one injection area to another (e.g. the abdominal wall compared with the thigh). The puncture site within a given injection area must be changed regularly (generally, every 1 to 3 days) in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients hypersensitive to Insuman Infusat for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – where necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin intradermal skin testing is recommended prior to a transfer to Insuman Infusat, since they may experience immunological cross-reactions.

In case of hypoglycaemia, the insulin pump should temporarily be turned off, at least until the patient has recovered complete consciousness.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Transfer to Insuman Infusat
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following transfer from an animal insulin to human insulin, dose regimen reduction may be required in particular in patients who
- were previously already controlled on rather low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transfer under medical supervision in a hospital or similar setting must be considered.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the

patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:
- change in the injection area,
- improved insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Insulin pump faults
Hyperglycaemia, ketoacidosis and coma may develop within hours if the pump catheter is obstructed completely. Whenever the patient notices a rapid increase in blood glucose which does not respond to a bolus dose, a check must be made for possible catheter obstruction.

In the event of a pump malfunction, patients must always have injection devices (injection syringe or pen) and insulin available for subcutaneous injection. For details on safety precautions in the use of insulin pumps, refer to the operator’s manual.

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Medication errors
Medication errors have been reported in which other Insuman formulations or other insulins have been accidentally administered. Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins.

Combination of Insuman with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insuman is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline,

propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human, no clinical data on exposed pregnancies are available. Insulin does not cross the placental barrier. Caution should be exercised when prescribing to pregnant women.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the suckling child are anticipated. Insuman Infusat can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. In clinical studies and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	Common	Uncommon	Not known
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Oedema		Hypoglycaemia; Sodium retention
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Skin and subcutaneous tissue disorders			Lipodystrophy; Cutaneous amyloidosis
General disorders and administration site conditions	Injection site reactions	Injection site urticaria	Injection site inflammation; Injection site pain; Injection site pruritus; Injection site erythema; Injection site swelling

Description of selected adverse reactions
Immune system disorders

Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Insulin administration may cause anti-insulin antibodies to form. In rare cases, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eyes disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

General disorders and administration site conditions
Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC Code: A10AB01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in themuscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insuman Infusat is an insulin with rapid onset and short duration of action.

5.2 Pharmacokinetic properties

In healthy subjects, the serum half-life of insulin is approximately 4 to 6 minutes. It is longer in patients with severe renal insufficiency. However, it must be noted that the pharmacokinetics of insulin do not reflect its metabolic action.

5.3 Preclinical safety data

The acute toxicity was studied following subcutaneous administration in rats. No evidence of toxic effects was found. Local tolerability studies following subcutaneous and intramuscular administration in rabbits gave no remarkable findings. Studies of pharmacodynamic effects following subcutaneous administration in rabbits and dogs revealed the expected hypoglycaemic reactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol,
zinc chloride,
trometamol,
poloxamer 171,
glycerol,
sodium hydroxide,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Insuman Infusat must not be mixed with solutions containing reducing substances such as thioles and sulphites.

Mixing of insulins
Insuman Infusat must not be mixed with any other insulin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution.

6.3 Shelf life

Insuman Infusat 100 IU/ml in a vial
3 years.

Insulin that has been filled into the pump reservoir may be used for two weeks thereafter.

Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks not above 25°C and away from direct heat or direct light.
Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use be noted on the label.

6.4 Special precautions for storage

Unopened vials Store in a
refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insuman Infusat next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Insuman Infusat 100 IU/ml in a vial
10 ml solution in a vial (type 1 colourless glass) with a flanged cap (aluminium), a stopper (chlorobutyl rubber (type 1)) and a tear-off cap (polypropylene).
Packs of 3 vials are available.

6.6 Special precautions for disposal and other handling

Insuman Infusat 100 IU/ml in a vial
Insuman Infusat must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of a water-like consistency.

For use in an infusion pump, Insuman Infusat in a vial is filled into the sterile cartridge of the pump. The cartridge must only be used once.

Before use, the filled cartridge must be kept at room temperature for 1 to 2 hours. Air bubbles must be removed before starting the infusion (see the operator's manual for the pump).

If the infusion pump malfunctions, the solution may be drawn from the cartridge into an injection syringe (suitable for an insulin with 100 IU/ml) and injected.

Insuman Infusat must not be used in peristaltic pumps with silicone tubing. Refer to the technical manual for contraindications relating to the use of insulin pumps.

It must be remembered that neutral regular insulin precipitates out at a pH of approximately 4.5 to 6.5.

Insulin label must always be checked before each injection to avoid medication errors between insulin human and other insulins (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Insuman Implantable 400 IU/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 400 IU insulin human* (equivalent to 14 mg).
One 10 ml vial of solution contains 4,000 IU insulin. One IU (International Unit) corresponds to 0.035 mg of anhydrous human insulin.

Insuman Implantable is a neutral insulin solution (regular insulin).
*Insulin human is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion (infusion).
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Insuman Implantable is indicated for the treatment of adult patients with type 1 diabetes mellitus that cannot be controlled with subcutaneous insulin (including pump) therapy, presenting with frequent, otherwise unexplained severe hyper-and/or hypoglycaemia.

4.2 Posology and method of administration

The prescription of this medicinal product is restricted to centres certified by Medtronic as having received adequate training in the use of the Medtronic MiniMed Implantable Pump.

Use of Insuman Implantable should be supervised by a physician experienced in diabetes and competent in using intraperitoneal insulin.

Posology

The desired blood glucose levels and the insulin dose regimen must be determined individually and adjusted to suit the patient's diet, physical activity and life-style. Frequent adjustments of insulin doses under strict medical supervision are often required for several weeks following pump implantation.

The pump is not connected to a glucose meter, and as such, patients are advised to practice good diabetes self management and test their own blood glucose levels at least four times daily to detect potential malfunction of the pump, to monitor glycaemic control and to determine required insulin doses.

Daily doses and timing of administration
There are no fixed rules for insulin dose regimen. A part of the daily insulin dose ("basal rate") is infused continuously by the implantable pump and the remaining part of the daily dose is administered by the patient, using the same pump, as a bolus before meals. The basal metabolic requirement is usually 40% to 60% of the total daily insulin requirement. Changes in basal and bolus doses are controlled by means of a small, hand held unit (Personal Pump Communicator (PPC)) which communicates with the pump via radio waves. The detailed operating instructions about the

implantable pump, its functions and the necessary safety precautions are described in the Physician's Manual accompanying the infusion pump.

Time of refill of insulin pump
The refill procedure should be performed every 40 to 45 days. The time between two refill procedures cannot exceed 45 days for insulin in-use stability reasons. Patients may require more frequent refill procedures based on their insulin needs.

Change to Insuman Implantable
Dose regimen adjustment may be necessary when changing patients from one insulin preparation to another. This applies, for example, when changing from:
- an animal insulin (especially a bovine insulin) to human insulin,
- one human insulin preparation to another,
- a regimen with only regular insulin to one with a longer-acting insulin.

The need to adjust (e.g. reduce) the dose may become evident immediately after transfer. Alternatively, it may emerge gradually over a period of several weeks.

Following the change from an animal insulin to human insulin, dose reduction may be required in particular in patients who:
- were already controlled with relatively low blood glucose levels,
- have a tendency to hypoglycaemia,
- previously required high insulin doses due to the presence of insulin antibodies.

Close metabolic monitoring is recommended during the transition and in the initial weeks thereafter. In patients who require high insulin doses because of the presence of insulin antibodies, transition under medical supervision in a hospital or similar setting must be considered.

Secondary dose adjustment
Improved metabolic control may result in increased insulin sensitivity, leading to a reduced insulin requirement. Dose adjustment may also be required, for example, if:
- the patient's weight changes,
- the patient's life-style changes,
- other circumstances arise that may promote an increased susceptibility to hypo- or hyperglycaemia (see section 4.4).

Special populations
Elderly population (≥65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment
In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Paediatric population
No data are available. Therefore, the safety and efficacy of Insuman Implantable (intraperitoneal use) have not been established in paediatric patients. In patients who have not reached adult size, Insuman Implantable is contraindicated (see section 4.3 and 4.4).

Method of administration
Insuman Implantable is to be used in the Medtronic MiniMed Implantable pump only.
Insuman Implantable is for intraperitoneal use only. Other routes of administration (e.g. injection) are contraindicated.

Insuman Implantable has been designed only for intraperitoneal use with the Medtronic MiniMed Implantable Pump supplied by Medtronic MiniMed which delivers insulin directly into the peritoneal cavity.
Insuman Implantable must not be used with any other pumps (external or implantable) than the Medtronic MiniMed Implantable pump or with any other medical devices including syringes (see section 6.6).

Pump refill
The pump refill procedure should be performed using sterile technique and this should take place in the centres certified by Medtronic. Reservoir refilling must be performed by trained and qualified personnel in accordance with the instructions provided by the pump manufacturer. The healthcare institution's standard sterile operating procedures for skin preparation must be followed to avoid microbial contamination and infection. All solutions that will enter the pump must be properly degassed prior to filling the pump reservoir to avoid insulin aggregation and under-delivery. The vials of insulin should be withdrawn from the refrigerator and stored at room temperature in the outer carton in order to protect from light for a minimum of 4 hours and no longer than 24 hours before use. The insulin solution must be then degassed according to the degassing procedure described in the Physician's manual.
In this refilling procedure the remaining insulin must be removed from the pump and the pump refilled with new insulin. The reservoir is completely filled (approximately 15 ml or 6,000 units of Insuman Implantable), independently of the patients needs. Residual insulin and new insulin must be weighed to record the refill worksheet and calculate the refill accuracy criterion. For further details on handling see section 6.6 and instructions provided in the Physician's manual.

Rinsing of the pump
All solutions that will enter the pump must be properly degassed prior to filling the pump reservoir to avoid insulin aggregation and under-delivery.
A rinse procedure using 0.1 M sodium hydroxide solution is performed to dissolve insulin deposits within the pump reservoir, pumping mechanism and the side port catheter. It is recommended to perform the rinse procedure every 6 months.
Rinsing may be performed earlier, for example if insulin under-delivery is revealed during a refill procedure or suspected due to insufficient blood glucose control. Diagnostic procedures must be performed to check if the problem is due to the pump or catheter.

- When under-delivery of insulin is due to catheter occlusion, the side port catheter may be flushed with 5-10 ml of sterile rinse buffer solution.
- When under-delivery is caused by a problem with the pump, a rinse procedure should be performed.

For further details on handling see section 6.6 and instructions provided in the Physician's manual.

Insuman Implantable is a high-concentrated insulin formulation
Insuman Implantable contains 400 international units of insulin in each ml.
The label on the insulin vial should be checked before use to make sure this is the correct insulin for the intended route of administration.

Patients should be informed about the high concentration of insulin in Insuman Implantable (400 IU/ml) compared to other insulins in vials or cartridges (usually 100 IU/ml).

Mixing of insulin
Insuman Implantable must not be mixed with any other insulin or with insulin analogues.

4.3 Contraindications

Insuman Implantable
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Other routes of administration (e.g. injection).

Medtronic MiniMed Implantable Pump
Hypersensitivity to titanium alloy, polysulfone or silicone materials used in the implanted components of the pump.
Use of other insulin medicinal products with the Medtronic MiniMed Implantable Pump.
Use in paediatric patients who have not reached adult size due to the large size of the pump (see section 4.2 and 4.4).
Implantation of the pump in patients who reside permanently at elevations above 2439 meters (8000 feet) (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

The Medtronic MiniMed Implantable Pump should not be implanted in patients who have medical or mental conditions that make them unable to program modifications to the pump based on glucose readings or to take appropriate corrective actions in case of pump system problems.

Patients implanted with a Medtronic MiniMed Implantable Pump must receive comprehensive instruction in the use of the pump, and the necessary actions in case of illness, hypoglycaemia and hyperglycaemia or pump failure. The patient should read and follow the instructions in the Patient Manual accompanying the infusion pump. For further details on handling see section 6.6.

Medical imaging technique
Patients who expect to need frequent or routine MRI or therapeutic ultrasound should not be implanted with the Medtronic MiniMed Implantable Pump.

Hypersensitivity
Patients hypersensitive to Insuman Implantable for whom no better tolerated preparation is available must only continue treatment under close medical supervision and – if necessary – in conjunction with anti-allergic treatment.

In patients with an allergy to animal insulin, intradermal skin testing is recommended prior to changing to Insuman Implantable, since they may experience immunological cross-reactions.
In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen and all other relevant factors must be reviewed before dose adjustment is considered.

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement.

Clinically relevant over-delivery of insulin was not observed during a 4 year period of evaluation of the Medtronic MiniMed Implantable Pump; however, this does not exclude the potential for such an occurrence.
In case of severe hypoglycaemia, patients should immediately contact their physician trained to perform pump investigations and the pump should then be investigated by the physician for possible catheter occlusion leading to accumulation of insulin with subsequent release of this accumulated insulin (see section 6.6).
During a refill procedure, a very small amount of insulin may be deposited subcutaneously, possibly resulting in hypoglycaemia. Patients must be informed to closely monitor blood glucose levels on refill days (see section 6.6).

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:

- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose regimen and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:

- improved insulin sensitivity (e.g., by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Hyperglycaemia

It is known that insulin can form aggregates, fibrils and gel-like structures when it is subjected to chemical and/or physical stress, e.g. increased temperatures and shaking. This can lead to obstruction of the implantable pump and under-delivery of insulin. Hyperglycaemia, ketoacidosis or coma may develop within hours in case of malfunction of the pump system. As soon as patients notice a rapid increase in blood glucose, which does not respond to a bolus dose of insulin, the possibility of pump obstruction should be investigated by a physician trained to perform pump investigations.
The patient should correct resistant hyperglycaemia with a standard dose of subcutaneous insulin.

Rinsing of pump to avoid insulin under-delivery

To avoid under-delivery which may occur when insulin deposits collect in the pumping mechanism inside the pump, it is recommended to follow a rinse procedure every 6 months. Rinsing may be performed earlier, for example, when potential under-delivery is suspected based on a calculated refill accuracy of less than 85%. Potential under-delivery of insulin by the Medtronic MiniMed Implantable Pump may result in an increase in daily programmed insulin usage, difficulty maintaining euglycaemia, refractory hyperglycaemia, and steady decrease in refill accuracy. Please refer to section 6.6 and the Physician’s Manual, which describe how to diagnose potential pump system problems that may cause insulin under-delivery, and how to correct and prevent under-delivery.

The majority of adverse reactions associated with the Medtronic MiniMed Implantable Pump can be prevented by the rinse procedure by physicians. Patients should practice good diabetes self care and check their blood glucose a minimum of 4 times daily to detect and prevent hyperglycemia and possible diabetic ketoacidosis due to pump under-delivery.
The patient plays a significant role in diagnosing and correcting hyperglycemia linked to pump performance problems. Should pump performance change, the patient would be able to detect a change in blood glucose levels.
In case of malfunction of the pump, patients should always have available injection devices (syringe or pen) and insulin suitable for subcutaneous injection.

Travel
The Medtronic MiniMed Implantable Pump is not designed for use at elevations above 2439 meters (8000 feet) or below 7.6 meters (25 feet). Use of the pump at these altitudes may result in insulin over-delivery or under-delivery.
Patients who reside permanently at elevations above 2439 meters (8000 feet) must not be implanted (see section 4.3).
Patients who plan to reside at or travel (other than by pressurised commercial aircraft) at elevations above 2439 meters (8000 feet) or to dive below 7.6 meters (25 feet) should be informed on the actions to be taken. The pump reservoir and Side Port catheter must be emptied of insulin and the patients must self-administer insulin by subcutaneous injection for the duration of the trip and until their pump reservoir is refilled.

The patient should be advised by the physician what needs to be done in case of travel, e.g. what to do if the pump malfunctions, availability of insulin and facility to replace the insulin, and who to contact in case of emergency. The patient should also be provided with alternative means of supplying insulin, e.g. provide the patient with 100 IU/ml insulin, devices, and supplies for subcutaneous injections.

Infection of the pump pocket
All procedures must be performed under sterile conditions. To avoid microbial contamination and infection, aseptic skin preparation should be performed according to the healthcare institution's standard sterile operating procedures. In addition, antibiotic prophylactic measures are required before and after pump implantation to reduce the risk of pump pocket infection. Failure to do so may result in pump pocket infection and subsequent pump explantation (see section 4.8).

Skin erosion
The implantable pump may erode through the skin, resulting in infection of the implant site and pump explantation. The risk of skin erosion at the pump implantation site can be reduced by selecting an appropriate implant site, maintaining good sterile technique during the implant procedure, prophylactic antibiotic therapy and by continuously wearing an abdominal binder until the capsule has formed (about 1 month) (see section 4.8).

Abnormal healing
Abnormal healing can occur at the surgical incision site after device implantation. This can be reduced by continuously wearing an abdominal binder until the capsule has formed (about 1 month) and limiting patient activities immediately following device implant.

Focal hepatic steatosis
Focal hepatic steatosis has been observed after administration of insulin via the intra-peritoneal route, when the catheter was positioned very close to or in the liver capsule. After stopping insulin infusion or removal or repositioning of the peritoneal catheter, focal hepatic steatosis seems to be reversible and without clinical consequence (see section 4.8).

Antibodies to insulin
The presence of antibodies has been reported in patients after treatment using the Medtronic MiniMed Implantable Pump. Insulin administration via the intraperitoneal route is likely to cause formation of anti-insulin antibodies. The presence of such insulin antibodies may necessitate adjustment of the insulin dose to correct a tendency for hyper- or hypoglycaemia (see section 4.8).

Intercurrent illness
Intercurrent illness requires intensified metabolic monitoring. In many cases, urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates (food or beverage) on a regular basis; even if they are able to eat only little or no food, or are vomiting, etc., and they must never omit insulin entirely.

Medication errors
Medication errors involving mix-up between subcutaneous Insuman formulations or other subcutaneous insulins have been reported. Insulin label must always be checked before each administration to avoid medication errors between Insuman Implantable and other insulins (see section 6.6).

Paediatric population
Due to the large size of the implantable pump, use of Insuman Implantable in paediatric patients who have not reached adult size is contraindicated (see section 4.2 and 4.3).

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin.

Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation

Pregnancy
For insulin human administered via subcutaneous route, no clinical data on exposed pregnancies are available. Insulin does not cross the placental barrier.

For Insuman Implantable administered via the intraperitoneal pump, the safety profile has not been established in pregnancy.
Women of childbearing potential, implanted or candidates for implantation, should inform their physician if they are contemplating pregnancy.
Caution should be exercised when prescribing to pregnant women. Insuman Implantable should not be used during pregnancy unless the clinical condition of the woman requires treatment with Insuman Implantable.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
No effects on the breastfed child are anticipated. Insuman Implantable can be used during breast-feeding. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
No clinical or animal data with insulin human on male or female fertility are available.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or use machines in these circumstances.

4.8 Undesirable effects

Summary of the safety profile
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. The frequency of this reaction varies with patient population and dose regimens.

Tabulated list of adverse reactions
From experience gained in a 6-month comparative phase III study (HUBIN_L_05335) with Insuman Implantable administered via the Medtronic MiniMed Implantable Pump in 84 patients aged 26 to 80 years (see section 5.1) and from clinical experience with insulin human 100 IU/ml and 40 IU/ml, the following adverse reactions were observed.

The following adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions observed in HUBIN_L_05335 study with insulin human 400 IU/ml and clinical experience with insulin human 100 IU/ml and 40 IU/ml.

MedDRA system organ classes	**Common**	**Uncommon**	**Not known**
Immune system disorders		Shock	Immediate type allergic reactions (hypotension, angioneurotic oedema, bronchospasm, generalised skin reactions); Anti-insulin antibodies
Metabolism and nutrition disorders	Hyperglycaemia; Hypoglycaemia; Hypoglycaemic seizure; Hypoglycaemic unconsciousness; ketosis; Oedema		Sodium retention
Nervous system disorders	Hypoglycaemic coma		
Eye disorders			Proliferative retinopathy; Diabetic retinopathy; Visual impairment
Hepatobiliary disorders			Focal hepatic steatosis (1)
(1) Adverse reaction observed with a semi-synthetic human insulin (400 IU/ml)			

The following related adverse reactions have been reported with the use of the Medtronic MiniMed Implantable Pump in the two phase III studies (see section 5.1).

Table 2: Adverse reactions and product technical complaints observed with the delivery system (including adverse reactions related to implantation surgery and or device maintenance).

MedDRA system organ classes	**Common**
Infections and infestations	Implant site infection (see section 4.4)
Gastrointestinal disorders	Abdominal pain Umbilical hernia
Skin and subcutaneous tissue disorders	Skin erosion at pump implantation site (see section 4.4)
General disorders and administration site conditions	Device occlusion; Catheter site pain
Surgical and medicinal procedures	Medical device change due to device malfunction Device blockage

Description of selected adverse reactions:
Immune system disorders
Immediate type allergic reactions to insulin or to the excipients may be life-threatening.

Anti-insulin antibodies: Limited data from a clinical trial with intraperitoneal administration of Insuman Implantable do not suggest that elevated levels of insulin antibodies are commonly associated with insulin antibody syndrome or serious adverse events (see section 4.4).

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Eye disorders
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.
Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

Hepatobiliary disorders
Focal hepatic steatosis has been reported in few patients receiving the semi-synthetic human insulin, when the catheter was in very close proximity to the liver.
When the catheter tip is fixed in the liver capsule, administration of insulin via the intra-peritoneal route is associated with an increased risk of focal hepatic steatosis (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose regimen of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

The physician must program specific limitations for insulin basal insulin rates, bolus delivery amounts. These limitations are necessary to provide some control over patients' ability to program their insulin regimens and to avoid the possibility of overdosing. In addition, if patients are attempting to deliver more than 2.5 times the programmed maximum bolus amount within a one hour period, the PPC will display the “HOURLY MAX EXCEEDED” message to warn the patients. Detailed instructions on programming these limitations are contained in the Physician’s Manual.

In case of severe hypoglycaemia, the pump should be investigated by the treating physician for possible catheter occlusion leading to accumulation of insulin with subsequent release of this accumulated insulin (see sections 4.4 and 6.6).

During a refill procedure, a very small amount of insulin may be deposited subcutaneously, possibly resulting in hypoglycaemia. Patients must be informed to closely monitor blood glucose levels on refill days (see section 6.6).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting.
ATC Code: A10AB01.

Mechanism of action
Insulin
- lowers blood glucose and promotes anabolic effects as well as decreasing catabolic effects,
- increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver, and improves pyruvate utilisation. It inhibits glycogenolysis and gluconeogenesis,
- increases lipogenesis in the liver and adipose tissue and inhibits lipolysis,
- promotes the uptake of amino acids into cells and promotes protein synthesis,
- enhances the uptake of potassium into cells.

Pharmacodynamic effects
Insuman Implantable is an insulin with rapid onset and short duration of action.

Clinical efficacy and safety
A single-blind, randomised, 6-month controlled clinical study (HUBIN_L_05335) was conducted to evaluate the clinical efficacy and safety of Insuman Implantable compared to a semi-synthetic human insulin (400 IU/ml) administered via the Medtronic MiniMed Implantable Pump. The study included 168 patients with type 1 diabetes mellitus, previously treated with the semi-synthetic human insulin. Before initial pump implantation, 72.4% of these patients had been treated by continuous subcutaneous insulin infusion (CSII) and 17.8% by subcutaneous multi-injection. Reasons for initiation of continuous intra-peritoneal insulin infusion (CIPII) were brittle diabetes in 62.7%, hypoglycaemia in 29.2%, insulin peripheral resistance in 5.0% and hypoglycaemia and brittle diabetes in 3.1%. At study initiation, half of the patients were switched to Insuman Implantable, while the other half remained on the semi-synthetic human insulin. The co-primary endpoint was change in HbA1c from baseline and the pump refill accuracy after 4 refill cycles (162 ± 21 days). Based on the change in HbA1c values from baseline, the glycaemic control in patients treated with Insuman Implantable was similar to that of patients treated with semi-synthetic human insulin. (per protocol population: -0.25 versus -0.12; [95% CI: -0.36; 0.11]). In addition, use of Insuman Implantable in continuous intraperitoneal infusion resulted in stable glycaemic control in patients with type 1 diabetes mellitus (per protocol population: mean reduction: -0.25 ± 0.67; [95% CI: -0.36; 0.11]) without increasing the risk of severe hypoglycaemia compared to semi-synthetic human insulin (14.3% versus 13.1%). Insuman Implantable administered in continuous intraperitoneal infusion was also similar to semi-synthetic human insulin as demonstrated by the refill accuracy criteria over the 4-refill cycles (per protocol population: mean difference: -3.15 ± 1.34; [95% CI: -5.81; -0.50]).

There was an additional 12-month open-label randomised controlled study (MIP 310) to assess the effect of intraperitoneal insulin administration versus subcutaneous insulin administration on glycaemic control and the frequency of severe hypoglycaemia. All patients were naive to intraperitoneal insulin and had failed to improve their HbA1c within 3 months of intensive therapy with either multiple daily injection or continuous subcutaneous insulin infusion. Mean HbA1c value at baseline was 8.1%. Patients enrolled in the continuous intraperitoneal insulin infusion group received The semi-synthetic human insulin 400 IU/ml for 180 days followed by Insuman Implantable 400 IU/ml for a further 180 days. Intraperitoneal insulin administration was similar to subcutaneous administration as demonstrated by change in HbA1c value from baseline (for continuous intraperitoneal administration: HbA1c value at Day 360 was 7.78 ± 1.04 versus 8.06 ± 0.77 at

baseline; for subcutaneous administration: HbA1c value at Day 360 was 8.19 ± 0.87 versus 8.12 ± 0.76 at baseline).

5.2 Pharmacokinetic properties

In literature, insulin pharmacokinetics are generally described to be reproducible in patients with type 1 diabetes mellitus receiving short-term and long-term continuous intraperitoneal insulin infusion. Continuous intraperitoneal insulin infusion results in earlier, shorter and higher peaks of plasma free insulin than continuous subcutaneous insulin infusion in patients with type 1 and type 2 diabetes mellitus.
Continuous infusion via the intraperitoneal and intravenous routes (combined data) resulted in higher plasma free insulin C_{max} values than multiple daily subcutaneous injections and continuous subcutaneous insulin infusion via an external pump (combined data) in patients with type 1 diabetes mellitus.
All of the findings suggest that continuous intraperitoneal insulin infusion in patients with type 1 diabetes mellitus, compared with continuous subcutaneous insulin infusion and multiple daily injections is more similar to the pharmacokinetics of endogenous insulin observed.

No food effect is expected on C_{max}, T_{max} and AUC values following CIPII administration.

In a phase III study (HUBIN_L_05335) in patients with type 1 diabetes mellitus, the pharmacokinetic profile of Insuman Implantable after intraperitoneal administration of an insulin bolus was assessed in 10 patients after intraperitoneal administration.

Absorption
After intraperitoneal administration of Insuman Implantable 0.15 IU/kg, the median T_{max} was 0.54 hours and C_{max} in serum was 210 ± 129 microIU/ml.
The mean pharmacokinetic profile is shown in figure 1.

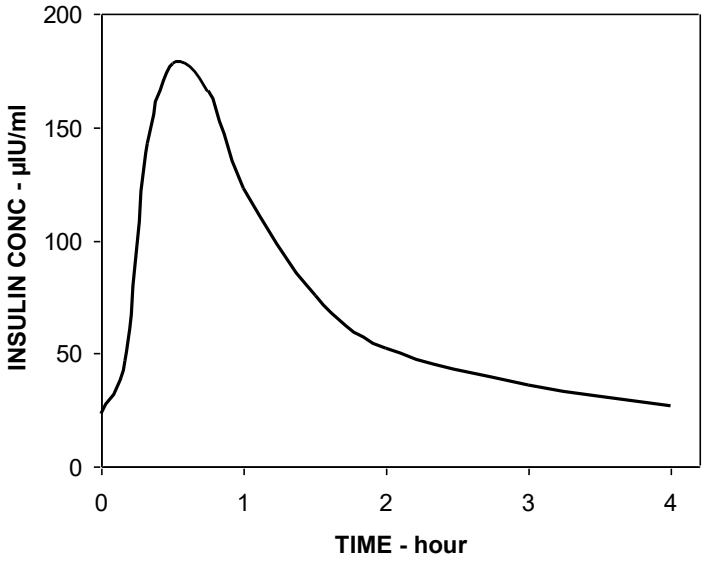

Figure 1: Mean pharmacokinetic profile of serum insulin in patients with type 1 diabetes mellitus after a dose of 0.15 IU/kg Insuman Implantable.

Elimination
After intraperitoneal administration of 0.15 IU/kg Insuman Implantable, insulin was eliminated from serum with an apparent mean half-life of 2.7 hours.

5.3 Preclinical safety data

Acute toxicity of insulin human was studied following subcutaneous administration in rats. No evidence of toxic effects was found.
No non-clinical studies assessing the potential toxicity of Insuman Implantable 400 IU/ml administered via intraperitoneal route were performed. However, three studies were conducted in rats to assess the potential toxicity of administration of human insulin via the intraperitoneal route. In a single-dose study in rats, a semi-synthetic insulin human in a formulation with 400 IU/ml and excipients identical to the Insuman Implantable 400 IU/ml formulation was administered by intraperitoneal injection. No clinical symptoms, macroscopically visible changes or irritations in the abdominal cavity were observed. In another study, rats also received the same semi-synthetic insulin via an intraperitoneally implanted osmotic mini-pump infusion for up to 6 weeks. No hepatic steatosis was observed. In a third study conducted in diabetic rats, administration of another human insulin with a formulation similar to Insuman via a catheter fixed to the liver capsule showed that intraperitoneal administration of high local insulin concentration at the liver capsule may induce reversible focal hepatic steatosis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol,
zinc chloride,
trometamol,
poloxamer 171,
glycerol,
hydrochloric acid (for pH adjustment),
sodium hydroxide (for pH adjustment),
water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Mixing of insulins
Insuman Implantable must NOT be mixed with any other insulin or with insulin analogues.

Care must be taken to ensure that no alcohol or other disinfectants enter the insulin solution.

6.3 Shelf life

2 years.

Shelf life in the pump
Up to 45 days at 37°C.

6.4 Special precautions for storage

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Insuman Implantable next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Shelf life in the pump
For in-use stability, see section 6.3.

6.5 Nature and contents of container

Colourless glass vial (type I) closed with flanged cap made of aluminium with tear-off lid and inserted sealing disk made of chlorobutyl rubber.
Each vial contains 10 ml of solution.
Packs of 1 and 5 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution must only be used if it is clear, colourless or almost colourless and practically free from visible particles.

Insulin label must always be checked before each administration to avoid medication errors between Insuman Implantable and other insulins (see section 4.4).

Insuman Implantable must not be used with any other pumps (external or implantable) than the Medtronic MiniMed Implantable pump or with any other medical devices including syringes (see section 4.2).

All procedures should be performed using sterile technique. Aseptic skin preparation should be performed according to the healthcare institution's standard sterile operating procedures to avoid microbial contamination and infection. Failure to do so may result in pump pocket infection and subsequent pump explantation (see section 4.4).

All solutions that will enter the pump must be properly degassed prior to filling the pump reservoir to avoid insulin aggregation and under-delivery.The vials of insulin should be withdrawn from the refrigerator and stored at room temperature in the outer carton in order to protect from light for a minimum of 4 hours and no longer than 24 hours before use, to ensure further efficient degassing by following the procedure described in the Physician's manual. Failure to properly degas all fluids may introduce air in the pump causing insulin aggregation and under-delivery.

Pump refill
The pump reservoir stores about 6,000 units of insulin and requires a refill procedure every 40 to 45 days for insulin in-use stability reasons in the pump or earlier based on the insulin needs of the patients.

This procedure should always be scheduled in advance of PPC "low reservoir" or "empty reservoir" messages with the patient.

Only Insuman Implantable which has been specifically formulated for use in the Medtronic MiniMed Implantable Pump should be used to fill the sterile pump reservoir. Two vials of Insuman Implantable (2 x 10 ml) are required to completely refill the pump reservoir and exclude air from entering the pump reservoir during the refill procedure. Any unused insulin should be disposed of in accordance with local requirements and should not be reused.

Only the refill kit (syringe and stopcock), refill needles, port locating template supplied by Medtronic MiniMed and sterile rinse buffer solution manufactured by Sanofi-Aventis Deutschland GmbH should be used with Insuman Implantable to refill the pump reservoir.

During a refill procedure, never push in the refill syringe plunger to fill the pump. When the refill needle is properly seated in the pump fill port, then the vacuum in the pump reservoir will passively draw the insulin from the syringe into the pump reservoir. Failure of the insulin to enter the pump may indicate that the pump reservoir is still full. It may also indicate that the refill needle is not properly seated in the pump inlet valve. Pushing insulin in this circumstance could result in unintended insulin delivery to the subcutaneous tissue around the pump fill port.

During a refill procedure, a very small amount of insulin may be deposited subcutaneously, possibly resulting in hypoglycemia. Patients must be informed to closely monitor blood glucose levels on refill days.

During the refill procedure it is important to fill out the refill worksheet and to calculate refill accuracy to evaluate system function. A calculated refill accuracy of less than 85% is indicative of insulin under-delivery.

Detailed instructions on the refill procedure are contained in the Physician's Manual.

Insulin under-delivery

Insulin under-delivery is suspected when:

- The patient reports an increase in insulin use to maintain euglycaemia. This can be verified by checking the insulin daily history on the PPC at each visit.
- Refractory hyperglycaemia occurs.
- A refill accuracy of less than 85% is calculated during a refill procedure.

If insulin under-delivery is revealed during a refill procedure or suspected due to insufficient blood glucose control, diagnostic procedures must be performed to check if the problem is due to the pump (i.e. jammed pumping mechanism/backflow) or catheter (i.e. catheter occlusion). The stroke volume measurement procedure tests pump function, while a catheter flush procedure tests catheter patency. A stroke volume of between 0.42 µl to 0.58 µl without backflow is indicative of a catheter occlusion. Otherwise stroke volume values outside this range or the detection of backflow is indicative of a pump problem.

Under-delivery of insulin caused by catheter occlusion

Under-delivery caused by Side Port Catheter occlusion can occur either abruptly or gradually. The insulin usage and clinical symptoms may be identical to those of pump under-delivery. In addition, formation of a biofilm over the tip of the Side Port Catheter may cause latent hypoglycemia as the insulin programmed over time is trapped in the biofilm and is released after a sufficient volume of insulin has accumulated. A catheter flush procedure should be performed to clear the occlusion.

The catheter is flushed by using 5-10 ml of sterile rinse buffer solution.
Only the refill kit (syringe and stopcock), refill needles, port locating template supplied by Medtronic MiniMed and sterile rinse buffer solution manufactured by Sanofi-Aventis Deutschland GmbH should be used with Insuman Implantable to flush the catheter.

The catheter flush procedure should only be performed after confirming the stroke volume measurement. Failure to do this may cause permanent damage to the pump.

During the catheter flush procedure 13 units of insulin are manually pushed through the catheter and delivered to the patient. The patient must be closely monitored for possible hypoglycaemia and administered intravenous glucose or glycogen as needed.

After flushing and refill of the pump with insulin, about 13 units of the sterile rinse buffer solution will remain in the distal portion of the side port catheter. Depending on blood glucose values, an appropriate bolus amount must be programmed to remove the sterile rinse buffer solution from the catheter. The patient blood glucose levels must be monitored at least every 15 minutes following the flush. The patient should only be released once blood glucose levels are stable and within the safe range.

If the flush procedure is unsuccessful, catheter replacement surgery is usually performed.
Detailed instructions on the side port catheter flush procedure is contained in the Physician's Manual.

Under-delivery due to a problem with the pump
A rinse procedure of the pump is performed to reverse this condition.
The purpose of this procedure is to dissolve insulin deposits within the pump reservoir, pumping mechanism and the side port catheter using 0.1 M sodium hydroxide sterile solution supplied by Medtronic MiniMed. It is recommended to perform the rinse procedure every 6 months or as necessary based on the refill accuracy criterion.

Only refill kit, refill needles, port locating template, 0.1 M sodium hydroxide sterile solution supplied by Medtronic MiniMed and sterile rinse buffer solution manufactured by Sanofi-Aventis Deutschland GmbH should be used with Insuman Implantable to rinse the pump.

If the rinse procedure fails to restore the stroke volume and accurate delivery, an extended rinse procedure needs to be performed.

Only after successful restoration of the stroke volume measurement can the catheter be flushed with the sterile rinse buffer solution and the pump refilled with insulin.
Detailed instructions on the rinse procedure are contained in the Physician's Manual.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/202
EU/1/97/030/203

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 1997
Date of latest renewal: 21 February 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDINGSUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
Brüningstraße 50
D-65926 Frankfurt / Main
Germany

Name and address of the manufacturer responsible for batch release

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst
Brüningstraße 50
D-65926 Frankfurt / Main
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Insuman (all presentations except Insuman Implantable):
Medicinal product subject to medical prescription.

Insuman Implantable 400 IU/ml presentation:
Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The marketing authorisation holder (MAH) shall submit PSURs for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The following conditions of the MA refer to the Insuman Implantable 400 IU/ml strength solution for infusion.

The MAH shall implement a controlled distribution system for the Insuman Implantable 400 IU/ml strength solutions for infusion to ensure that the medicinal product is only available to centres with current certification by Medtronic as having the appropriate facilities and staff who have received adequate training in the use of the Medtronic MiniMed Implantable Pump and the Personal Pump Communicator (PPC).

The MAH shall ensure that the training programme for centres includes the following key elements:
- Device components
- Patient selection criteria
- Warnings and precautions when using an implantable pump
- Device programming
- Refill procedure
- Rinse and flush procedure, stroke measurement and pump management including troubleshooting
- Alarms and messages displayed by the device and the appropriate actions to take
- Recognition of signs and symptoms of under or no delivery of insulin and the appropriate actions to take
- Recognition of signs and symptoms of severe hypoglycaemia and the appropriate actions to take
- Training of patients and the key information that patients need to be aware of
- Ensuring that each patient receives the patient manual, the patient quick guide and the important patient information leaflet for the Medtronic MiniMed implantable insulin pump system and the patient emergency information card
- Information on the risk management plan, the safety concerns and the risk minimisation measures
- Information on the registry including how to, and the importance of, entering patients in it
- Surgical aspects of implantation

The MAH shall ensure that all centres are adequately supplied with the following in the appropriate national language(s):
- SmPC and patient information leaflets
- Patient emergency information cards
- The important patient information leaflets for the Medtronic MiniMed implantable insulin pump system. The MAH shall ensure the patient information leaflets include the following key messages:
    - The system does not check your blood glucose; therefore you need to **check your blood glucose at least 4 times a day** according to the method and frequency recommended by your physician;
    - You need to program boluses and temporary basal rates with your PPC;
    - You need to replace the 1.5V AA battery in the PPC every 4 weeks.
    - Every 40 to 45 days, a refill of insulin at the hospital is needed.
    - Running a diagnostic test of your pump system is needed if you think the pump may have been damaged by water, a sporting incident, electrotherapy (cardiac defibrillator), diagnostic ultrasound or radiation (X-ray).
    - You need to carry the completed Patient Emergency Information Card with you always.
    - You need to carry alternative insulin and the means to administer it with you always.
    - You need to keep some form of fast-acting sugar with you at all times.

- Implantable Insulin Pump System: Patient manuals
- Implantable Insulin Pump system: Physician Manuals
- Physician quick guides on the main programming functions
- Patient quick guides on the main programming functions

These materials shall contain content closely similar to the mock-ups provided in the currently approved risk management plan annexes.

The MAH shall ensure that all patients receive training in the following key elements regarding the Insuman Implantable Pump 400 IU/ml:

- Patients' responsibilities regarding insulin treatment as well as refill frequency and maintenance of the pump as outlined in the key messages in the patient information leaflet;
- Training on how to set up the pump with the PPC;
- Conduct of all procedures required for the correct management and maintenance of the Medtronic MiniMed Implantable Pump and the PPC, including rinsing procedures and instructions as to how to handle messages, alarms and routine warnings issued by the PPC;
- The potential for surgical and clinical complications and how to respond in the event any such complications arise.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml and 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Rapid 100 IU/ml solution for injection in a vial

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and short duration of action.

3. LIST OF EXCIPIENTS

Excipients: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
1 vial of 5 ml
5 vials of 5 ml 1 vial of 10 ml 5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator. Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/028 (1 vial of 5 ml)
EU/1/97/030/029 (5 vials of 5 ml)
EU/1/97/030/196 (1 vial of 10 ml)
EU/1/97/030/197 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Rapid 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Rapid 100 IU/ml solution for injection

Insulin human

Subcutaneous or intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml
10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 40 IU/ml: 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Rapid 40 IU/ml solution for injection in a vial

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 40 IU (1.4 mg) insulin human.

Insulin with a rapid onset and short duration of action.

3. LIST OF EXCIPIENTS

Excipients: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous or intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator. Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/031 (1 vial of 10 ml)
EU/1/97/030/032 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Rapid 40

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Rapid 40 IU/ml solution for injection

Insulin human

Subcutaneous or intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS/3 ML CARTRIDGES

1. NAME OF THE MEDICINAL PRODUCT

Insuman Rapid 100 IU/ml solution for injection in a cartridge

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and short duration of action.

3. LIST OF EXCIPIENTS

Excipients: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
3 cartridges of 3 ml
4 cartridges of 3 ml 5 cartridges of 3 ml 6 cartridges of 3 ml 9 cartridges of 3 ml 10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insuman Rapid cartridges are to be used only with the pens: ClikSTAR, Tactipen, Autopen 24, AllStar, AllStar PRO, JuniorSTAR.
Not all of these pens may be marketed in your country.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/085 (3 cartridges of 3 ml)
EU/1/97/030/055 (4 cartridges of 3 ml)
EU/1/97/030/030 (5 cartridges of 3 ml)
EU/1/97/030/090 (6 cartridges of 3 ml)
EU/1/97/030/095 (9 cartridges of 3 ml)
EU/1/97/030/056 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Rapid

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Rapid 100 IU/ml solution for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insuman Rapid SoloStar 100 IU/ml solution for injection in a pre-filled pen

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and short duration of action.

3. LIST OF EXCIPIENTS

Excipients: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
3 pens of 3 ml
4 pens of 3 ml 5
pens of 3 ml 6
pens of 3 ml 9
pens of 3 ml 10
pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.
Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator. Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/140 (3 pens of 3 ml)
EU/1/97/030/141(4 pens of 3 ml)
EU/1/97/030/142 (5 pens of 3 ml)
EU/1/97/030/143 (6 pens of 3 ml)
EU/1/97/030/144(9 pens of 3 ml)
EU/1/97/030/145 (10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Rapid SoloStar

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Rapid SoloStar 100 IU/ml solution for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml and 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Basal 100 IU/ml suspension for injection in a vial

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
1 vial of 5 ml
5 vials of 5 ml 1 vial of 10 ml 5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/033 (1 vial of 5 ml)
EU/1/97/030/034 (5 vials of 5 ml)
EU/1/97/030/198 (1 vial of 10 ml)
EU/1/97/030/199 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Basal 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Basal 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml
10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 40 IU/ml: 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Basal 40 IU/ml suspension for injection in a vial

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 40 IU (1.4 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/036 (1 vial of 10 ml)
EU/1/97/030/037 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Basal 40

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Basal 40 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insuman Basal 100 IU/ml suspension for injection in a cartridge

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
3 cartridges of 3 ml
4 cartridges of 3 ml 5 cartridges of 3 ml 6 cartridges of 3 ml 9 cartridges of 3 ml 10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insuman Basal cartridges are to be used only with the pens: ClikSTAR, Tactipen, Autopen 24, AllStar, AllStar PRO, JuniorSTAR.
Not all of these pens may be marketed in your country.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/086 (3 cartridges of 3 ml)
EU/1/97/030/057 (4 cartridges of 3 ml)
EU/1/97/030/035 (5 cartridges of 3 ml)
EU/1/97/030/091(6 cartridges of 3 ml)
EU/1/97/030/096 (9 cartridges of 3 ml)
EU/1/97/030/058 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Basal

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Basal 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insuman Basal SoloStar 100 IU/ml suspension for injection in a pre-filled pen

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
3 pens of 3 ml
4 pens of 3 ml 5
pens of 3 ml 6
pens of 3 ml 9
pens of 3 ml 10
pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/146 (3 pens of 3 ml)
EU/1/97/030/147 (4 pens of 3 ml)
EU/1/97/030/148 (5 pens of 3 ml)
EU/1/97/030/149 (6 pens of 3 ml)
EU/1/97/030/150 (9 pens of 3 ml)
EU/1/97/030/151 (10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Basal SoloStar

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Basal SoloStar 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 15 100 IU/ml suspension for injection in a vial

Insulin human

15% dissolved insulin, 85% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
1 vial of 5 ml
5 vials of 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/038 (1 vial of 5 ml)
EU/1/97/030/039 (5 vials of 5 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 15 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 15 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 15 100 IU/ml suspension for injection in a cartridge

Insulin human

15% dissolved insulin, 85% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
3 cartridges of 3 ml
4 cartridges of 3 ml 5 cartridges of 3 ml 6 cartridges of 3 ml 9 cartridges of 3 ml 10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insuman Comb 15 cartridges are to be used only with the pens: ClikSTAR, Tactipen, Autopen 24, AllStar, AllStar PRO, JuniorSTAR.
Not all of these pens may be marketed in your country.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/087 (3 cartridges of 3 ml)
EU/1/97/030/059 (4 cartridges of 3 ml)
EU/1/97/030/040 (5 cartridges of 3 ml)
EU/1/97/030/092 (6 cartridges of 3 ml)
EU/1/97/030/097 (9 cartridges of 3 ml)
EU/1/97/030/060 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 15

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 15 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 15 SoloStar 100 IU/ml suspension for injection in a pre-filled pen

Insulin human

15% dissolved insulin, 85% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
3 pens of 3 ml
4 pens of 3 ml 5 pens of 3 ml 6 pens of 3 ml 9 pens of 3 ml 10 pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/152 (3 pens of 3 ml)
EU/1/97/030/153(4 pens of 3 ml)
EU/1/97/030/154(5 pens of 3 ml)
EU/1/97/030/155(6 pens of 3 ml)
EU/1/97/030/156 (9 pens of 3 ml)
EU/1/97/030/157(10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 15 SoloStar

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 15 SoloStar 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 25 100 IU/ml suspension for injection in a vial

Insulin human

25% dissolved insulin, 75% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
1 vial of 5 ml
5 vials of 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/043 (1 vial of 5 ml)
EU/1/97/030/044 (5 vials of 5 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 25 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 25 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 40 IU/ml: 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 25 40 IU/ml suspension for injection in a vial

Insulin human

25% dissolved insulin, 75% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 40 IU (1.4 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/046 (1 vial of 10 ml)
EU/1/97/030/047 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 25 40

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 25 40 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 25 100 IU/ml suspension for injection in a cartridge

Insulin human

25% dissolved insulin, 75% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
3 cartridges of 3 ml
4 cartridges of 3 ml 5 cartridges of 3 ml 6 cartridges of 3 ml 9 cartridges of 3 ml 10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insuman Comb 25 cartridges are to be used only with the pens: ClikSTAR, Tactipen, Autopen 24, AllStar, AllStar PRO, JuniorSTAR.
Not all of these pens may be marketed in your country.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/088 (3 cartridges of 3 ml)
EU/1/97/030/061 (4 cartridges of 3 ml)
EU/1/97/030/045 (5 cartridges of 3 ml)
EU/1/97/030/093 (6 cartridges of 3 ml)
EU/1/97/030/098 (9 cartridges of 3 ml)
EU/1/97/030/062 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 25

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 25 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 25 SoloStar 100 IU/ml suspension for injection in a pre-filled pen

Insulin human

25% dissolved insulin, 75% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
3 pens of 3 ml
4 pens of 3 ml 5
pens of 3 ml 6
pens of 3 ml 9
pens of 3 ml 10
pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGH AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/158 (3 pens of 3 ml)
EU/1/97/030/159 (4 pens of 3 ml)
EU/1/97/030/160 (5 pens of 3 ml)
EU/1/97/030/161 (6 pens of 3 ml)
EU/1/97/030/162 (9 pens of 3 ml)
EU/1/97/030/163(10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 25 SoloStar

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 25 SoloStar 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml and 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 30 100 IU/ml suspension for injection in a vial

Insulin human

30% dissolved insulin, 70% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
1 vial of 5 ml
5 vials of 5 ml 1 vial of 10 ml 5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/170(1 vial of 5 ml)
EU/1/97/030/171(5 vials of 5 ml)
EU/1/97/030/200 (1 vial of 10 ml)
EU/1/97/030/201 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 30 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 30 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml
10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 30 100 IU/ml suspension for injection in a cartridge

Insulin human

30% dissolved insulin, 70% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
3 cartridges of 3 ml
4 cartridges of 3 ml 5 cartridges of 3 ml 6 cartridges of 3 ml 9 cartridges of 3 ml 10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insuman Comb 30 cartridges are to be used only with the pens: ClikSTAR, Tactipen, Autopen 24, AllStar, AllStar PRO, JuniorSTAR.
Not all of these pens may be marketed in your country.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/172 (3 cartridges of 3 ml)
EU/1/97/030/173 (4 cartridges of 3 ml)
EU/1/97/030/174(5 cartridges of 3 ml)
EU/1/97/030/175 (6 cartridges of 3 ml)
EU/1/97/030/176 (9 cartridges of 3 ml)
EU/1/97/030/177 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 30

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 30 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 30 SoloStar 100 IU/ml suspension for injection in a pre-filled pen

Insulin human

30% dissolved insulin, 70% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a gradual onset and long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
3 pens of 3 ml
4 pens of 3 ml 5
pens of 3 ml 6
pens of 3 ml 9
pens of 3 ml 10
pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/190 (3 pens of 3 ml)
EU/1/97/030/191 (4 pens of 3 ml)
EU/1/97/030/192 (5 pens of 3 ml)
EU/1/97/030/193 (6 pens of 3 ml)
EU/1/97/030/194 (9 pens of 3 ml)
EU/1/97/030/195 (10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 30 SoloStar

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 30 SoloStar 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 100 IU/ml: 5 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 50 100 IU/ml suspension for injection in a vial

Insulin human

50% dissolved insulin, 50% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and moderately long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
1 vial of 5 ml
5 vials of 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/048 (1 vial of 5 ml)
EU/1/97/030/049 (5 vials of 5 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 50 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 50 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / FOR 40 IU/ml: 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 50 40 IU/ml suspension for injection in a vial

Insulin human

50% dissolved insulin, 50% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 40 IU (1.4 mg) insulin human.

Insulin with a rapid onset and moderately long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
1 vial of 10 ml
5 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.

8. EXPIRY DATE

EXP

Once in-use, vials may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/051 (1 vial of 10 ml)
EU/1/97/030/052 (5 vials of 10 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 50 40

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 50 40 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 50 100 IU/ml suspension for injection in a cartridge

Insulin human

50% dissolved insulin, 50% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and moderately long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
3 cartridges of 3 ml
4 cartridges of 3 ml 5 cartridges of 3 ml 6 cartridges of 3 ml 9 cartridges of 3 ml 10 cartridges of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The Insuman Comb 50 cartridges are to be used only with the pens: ClikSTAR, Tactipen, Autopen 24, AllStar, AllStar PRO, JuniorSTAR.
Not all of these pens may be marketed in your country.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

Once in-use, cartridges may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use (in the pen), do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze. Keep the cartridge in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/089 (3 cartridges of 3 ml)
EU/1/97/030/063 (4 cartridges of 3 ml)
EU/1/97/030/050 (5 cartridges of 3 ml)
EU/1/97/030/094 (6 cartridges of 3 ml)
EU/1/97/030/099 (9 cartridges of 3 ml)
EU/1/97/030/064 (10 cartridges of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 50

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TEXT TO APPEAR ON THE ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 50 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Use specific pens: see leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 3 ML PRE-FILLED PEN SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT

Insuman Comb 50 SoloStar 100 IU/ml suspension for injection in a pre-filled pen

Insulin human

50% dissolved insulin, 50% crystalline protamine insulin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

Insulin with a rapid onset and moderately long duration of action.

3. LIST OF EXCIPIENTS

Excipients: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
3 pens of 3 ml
4 pens of 3 ml 5 pens of 3 ml 6 pens of 3 ml 9 pens of 3 ml 10 pens of 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Mix thoroughly.
Only use injection needles that have been approved for use with SoloStar.

8. EXPIRY DATE

EXP

Once in-use, pens may be kept for up to 4 weeks. Do not store above 25°C and protect from direct heat and light. When in-use, do not store in a refrigerator.

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze. Keep the pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/164 (3 pens of 3 ml)
EU/1/97/030/165 (4 pens of 3 ml)
EU/1/97/030/166 (5 pens of 3 ml)
EU/1/97/030/167(6 pens of 3 ml)
EU/1/97/030/168 (9 pens of 3 ml)
EU/1/97/030/169(10 pens of 3 ml)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Comb 50 SoloStar

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL SOLOSTAR

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Comb 50 SoloStar 100 IU/ml suspension for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 10 ML VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Infusat 100 IU/ml solution for injection in a vial

Insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 IU (3.5 mg) insulin human.

3. LIST OF EXCIPIENTS

Excipients: phenol, zinc chloride, trometamol, glycerol, poloxamer 171, sodium hydroxide, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
3 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use. For use in insulin pumps, which are suitable for insulins containing 100 IU/ml.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened vials:

Store in a refrigerator.
Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/053

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Insuman Infusat 100

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Infusat 100 IU/ml solution for injection

Insulin human

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTONS / 10 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT

Insuman Implantable 400 IU/ml solution for infusion

insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 400 IU insulin human (equivalent to 14 mg).

3. LIST OF EXCIPIENTS

Excipients: phenol, zinc chloride, trometamol, glycerol, poloxamer 171, sodium hydroxide, hydrochloric acid and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
4,000 IU/10 ml
1 vial
5 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Use only with Medtronic MiniMed Implantable Pump.

Single-use vial

Read the package leaflet before use.

Intraperitoneal use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CAUTION HIGH STRENGTH

Use only clear and colourless solutions.

Insulin with a rapid onset and short duration of action

8. EXPIRY DATE

EXP
In the pump, the medicine is stable for 45 days at 37°C.

9. SPECIAL STORAGE CONDITIONS

Unopened vials:
Store in a refrigerator. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/030/202 (1 vial of 10 ml)
EU/1/97/030/203 (5 vials of 10 ml)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Insuman Implantable 400 IU/ml infusion

insulin human

Intraperitoneal use

2. METHOD OF ADMINISTRATION

Use only with Medtronic MiniMed Implantable Pump.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4,000 IU/10 ml

6. OTHER

HIGH STRENGTH

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Insuman Rapid 100 IU/ml solution for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Rapid is and what it is used for

Insuman Rapid contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Rapid is an insulin solution with a rapid onset and short duration of action.

Insuman Rapid is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar. Insuman Rapid may also be used for treating hyperglycaemic coma (coma caused by too much blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar) as well as for controlling blood sugar before, during and after surgery.

2. What you need to know before you use Insuman Rapid

Do not use Insuman Rapid

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Rapid.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Rapid). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Rapid

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
  isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Rapid with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Rapid in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Rapid

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Rapid

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Rapid per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Rapid.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Rapid is injected under the skin 15 to 20 minutes before a meal.

Method of administration

Insuman Rapid is a solution for injection under the skin or, in exceptional circumstances, into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Insulin administration into a vein for example to treat severe hyperglycaemia and ketoacidosis, requires experience and special safety precautions. For these reasons, it must be done in a clinic or a similar setting.

Do not use Insuman Rapid in insulin pumps – special insulin preparations are available for use in such devices. Also do not use it in peristaltic pumps with silicone tubing.

How to handle the vials

Insuman Rapid contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Insuman Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and has a water-like consistency.

Do not shake the vial vigorously as this could cause froth to form. Froth can make it difficult for you to measure the correct dose.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Rapid may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw Insuman Rapid into the injection syringe before the other insulin. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Rapid than you should
- If you **have injected too much Insuman Rapid**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Rapid
- If you **have missed a dose of Insuman Rapid** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Rapid
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Rapid without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Rapid and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Rapid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Rapid next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Rapid contains
- The active substance is insulin human. One ml of Insuman Rapid contains 100 IU (International Units) of the active substance insulin human.

- The other ingredients are: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Rapid”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Rapid looks like and contents of the pack
Insuman Rapid is a clear, colourless solution for injection, with no solid particles visible, and of a water-like consistency.

Insuman Rapid is supplied in vials containing 5 ml of solution for injection (equivalent to 500 IU) or 10 ml of solution for injection (equivalent to 1000 IU). Packs of 1 and 5 vials of 5 ml or 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH Tel:
0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Rapid").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Rapid").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,

- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heartbeat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Rapid").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Rapid 40 IU/ml solution for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Rapid is and what it is used for

Insuman Rapid contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Rapid is an insulin solution with a rapid onset and short duration of action.

Insuman Rapid is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar. Insuman Rapid may also be used for treating hyperglycaemic coma (coma caused by too much blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar) as well as for controlling blood sugar before, during and after surgery.

2. What you need to know before you use Insuman Rapid

Do not use Insuman Rapid

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Rapid.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Rapid). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Rapid

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Rapid with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Rapid in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Rapid

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Rapid

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Rapid per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Rapid.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Rapid is injected under the skin 15 to 20 minutes before a meal.

Method of administration

Insuman Rapid is a solution for injection under the skin or, in exceptional circumstances, into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Insulin administration into a vein for example to treat severe hyperglycaemia and ketoacidosis, requires experience and special safety precautions. For these reasons, it must be done in a clinic or a similar setting.

Do not use Insuman Rapid in insulin pumps – special insulin preparations are available for use in such devices. Also do not use it in peristaltic pumps with silicone tubing.

How to handle the vials

Insuman Rapid contains 40 IU insulin per ml. Only injection syringes designed for this insulin concentration (40 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Insuman Rapid must only be used if the solution is clear, colourless, with no solid particles visible, and has a water-like consistency.

Do not shake the vial vigorously as this could cause froth to form. Froth can make it difficult for you to measure the correct dose.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Rapid may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw Insuman Rapid into the injection syringe before the other insulin. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Rapid than you should
- If you **have injected too much Insuman Rapid**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Rapid
- If you **have missed a dose of Insuman Rapid** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Rapid
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Rapid without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Rapid and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not know (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not know

- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.

- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.

- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Rapid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials

Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insuman Rapid next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials

Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Rapid contains

- The active substance is insulin human. One ml of Insuman Rapid contains 40 IU (International Units) of the active substance insulin human.

- The other ingredients are: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Rapid”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Rapid looks like and contents of the pack
Insuman Rapid is a clear, colourless solution for injection, with no solid particles visible, and of a water-like consistency.

Insuman Rapid is supplied in vials containing 10 ml solution (400 IU). Packs of 1 and 5 vials of 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH Tel:
0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Rapid").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Rapid").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,

- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.
The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Rapid").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Rapid 100 IU/ml solution for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Rapid is and what it is used for

Insuman Rapid contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Rapid is an insulin solution with a rapid onset and short duration of action.

Insuman Rapid is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Rapid

Do not use Insuman Rapid

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Rapid in cartridges is only suitable for injecting just under the skin using a reusable pen (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Rapid.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Rapid). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Rapid

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions orhigh blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Rapid with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Rapid in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Rapid

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Rapid

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Rapid per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Rapid.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Rapid is injected under the skin 15 to 20 minutes before a meal.

Method of administration

Insuman Rapid is a solution for injection under the skin.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use Insuman Rapid in insulin pumps - special insulin preparations are available for use in such devices. Also do not use it in peristaltic pumps with silicone tubing.

How to handle the cartridges

Insuman Rapid in cartridges is only suitable for injecting just under the skin using a reusable pen (see also section 3). Speak to your doctor if you need to inject your insulin by another method.
To ensure you get the accurate dose, the Insuman Rapid cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- ClikSTAR, Tactipen, Autopen 24, AllStar or AllStar PRO which deliver doses in steps of 1 unit.
Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer’s instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen.

Look at the cartridge before you use it. Only use it if the solution is clear, colourless, with no solid particles visible, and has a water-like consistency.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix Insuman Rapid with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If you use more Insuman Rapid than you should
- If you **have injected too much Insuman Rapid**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Rapid
- If you **have missed a dose of Insuman Rapid** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Rapid
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Rapid without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Rapid and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heartbeat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Rapid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Rapid next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Rapid contains
- The active substance is insulin human. One ml of Insuman Rapid contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insuman Rapid"), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Rapid looks like and contents of the pack
Insuman Rapid is a clear, colourless solution for injection, with no solid particles visible, and of a water-like consistency.

Insuman Rapid is supplied in cartridges containing 3 ml solution (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH Tel:
0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

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Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Rapid").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Rapid").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,

- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Rapid").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Rapid Solostar 100 IU/ml solution for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully including the Instructions for Use of Insuman Rapid SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Rapid is and what it is used for

Insuman Rapid contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Rapid is an insulin solution with a rapid onset and short duration of action. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insuman Rapid is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Rapid

Do not use Insuman Rapid

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Rapid in pre-filled pen is only suitable for injecting just under the skin (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Rapid.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins talk to your doctor.

Special patient groups

If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Rapid). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Rapid

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),

- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Rapid with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast feeding think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your babyHowever, there is no experience with the use of Insuman Rapid in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Rapid

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Rapid

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Rapid per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Rapid.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Rapid is injected under the skin 15 to 20 minutes before a meal.

Method of administration

Insuman Rapid is a solution for injection under the skin.

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing insulin human. Insuman Rapid in pre-filled pen is only suitable for injecting just under the skin. Speak to your doctor if you need to inject your insulin by another method.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.

A safety test must be performed before each injection.

Look at the cartridge before you use the pen. Do not use Insuman Rapid if you notice particles in it. Only use Insuman Rapid if the solution is clear, colourless and waterlike.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insuman Rapid Solostar pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly, it has to be discarded and a new SoloStar has to be used.

If you use more Insuman Rapid than you should
- If you **have injected too much Insuman Rapid**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Rapid
- If you **have missed a dose of Insuman Rapid** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Rapid
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Rapid without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Rapid and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Rapid.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Rapid contains
- The active substance is insulin human. One ml of Insuman Rapid contains 100 IU (International Units) of the active substance insulin human.

- The other ingredients are: metacresol, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Rapid”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Rapid looks like and contents of the pack
Insuman Rapid is a clear, colourless solution for injection, with no solid particles visible, and of a water-like consistency.

Insuman Rapid is supplied in pre-filled pens, SoloStar, containing 3 ml solution (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00 (Belgique/Belgien)

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
Sanofi-Aventis
Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A. Tel: +34 93 485 94 00

Polska
sanofi-aventis Sp. z o.o.

Tel.: +48

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger:
+33 1 57 63 23 23

Hrvatska
sanofi-aventis Croatia d.o.o.
Tel: +385 1 600 34 00

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

22 280 00 00

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Portugal
Sanofi - Produtos Farmacêuticos,
Lda. Tel: +351 21 35 89 400

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

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Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Rapid").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Rapid").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,

- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Rapid").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insuman Rapid SoloStar solution for injection in a pre-filled pen. Instructions for Use.

SoloStar is a pre-filled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

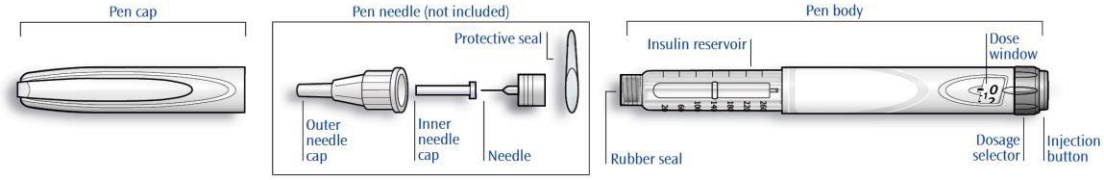
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or contact the local representative of the Marketing Authorization Holder mentioned on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. Insuman SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insuman insulin used. The pictures below are for illustrative purposes only.

B. Take off the pen cap.

C. Check the appearance of your insulin.
If you are using clear insulin (Insuman Rapid), do not use this pen if the insulin is cloudy, coloured or has particles.

Step 2. Attach the needle

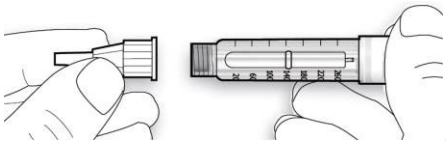
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of the needle, carefully read the “Instructions for Use” accompanying the needles.

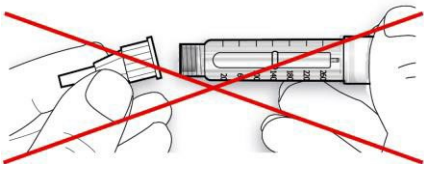
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



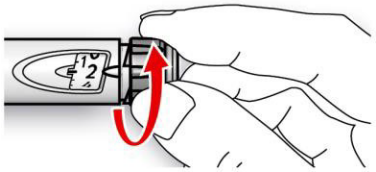
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



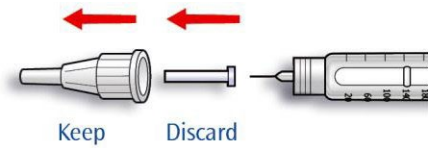
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



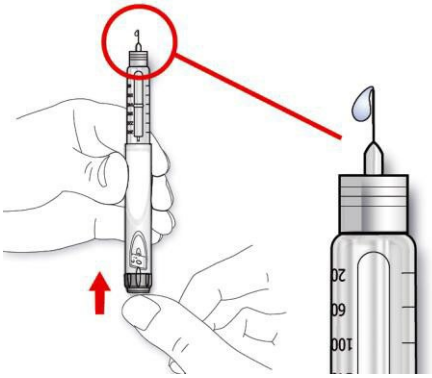
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

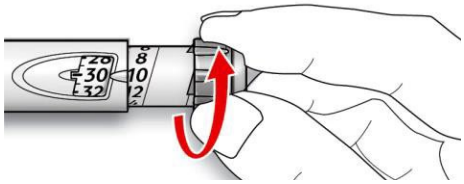
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



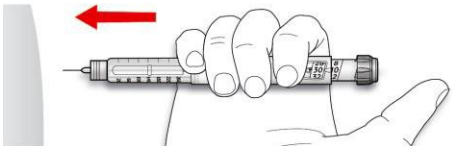
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

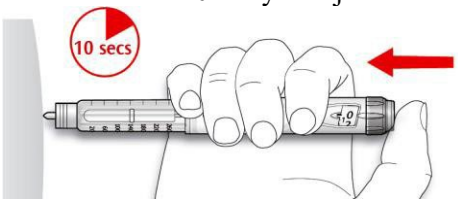
Step 5. Inject the dose

A. Use the injection method as instructed by your doctor, pharmacist or nurse.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to “0” as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin has been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:

- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up to room temperature. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet: Information for the user

Insuman Basal 100 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Basal is and what it is used for.

Insuman Basal contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Basal is an insulin preparation with a gradual onset and long duration of action. The insulin is present as tiny crystals of insulin protamine.

Insuman Basal is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Basal

Do not use Insuman Basal

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Basal
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Basal). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Basal

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Basal with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Basal in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Basal

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Basal

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Basal per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Basal.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Basal is injected under the skin 45 to 60 minutes before a meal.

Method of administration

Basal is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Basal into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the vials

Insuman Basal contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Basal may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparation. If you need to inject a mixture, draw the other insulin into the injection syringe before Insuman Basal. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Basal than you should
- If you **have injected too much Insuman Basal**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Basal
- If you **have missed a dose of Insuman Basal** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Basal
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Basal without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Basal and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antobodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Basal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insuman Basal next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Basal contains
- The active substance is insulin human. One ml of Insuman Basal contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium

dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insuman Basal"), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Basal looks like and contents of the pack
After mixing, Insuman Basal is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Basal is supplied in vials containing 5 ml of suspension for injection (equivalent to 500 IU) or 10 ml of suspension for injection (equivalent to 1000 IU). Packs of 1 and 5 vials of 5 ml or 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH Tel:
0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

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Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Basal").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Basal").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),

- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Basal").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Basal 40 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Basal is and what it is used for

Insuman Basal contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Basal is an insulin preparation with a gradual onset and long duration of action. The insulin is present as tiny crystals of insulin protamine.

Insuman Basal is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Basal

Do not use Insuman Basal

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Basal.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Basal). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early**.

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Basal

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Basal with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Basal in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Basal

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Basal

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Basal per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Basal.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Basal is injected under the skin 45 to 60 minutes before a meal.

Method of administration

Insuman Basal is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Basal into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the vials

Insuman Basal contains 40 IU insulin per ml. Only injection syringes designed for this insulin concentration (40 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Basal may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insuman Basal. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Basal than you should
- If you **have injected too much Insuman Basal**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Basal
- If you **have missed a dose of Insuman Basal** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Basal
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Basal without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Basal and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Basal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Basal next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Basal contains
- The active substance is insulin human. One ml of Insuman Basal contains 40 IU (International Units) of the active substance insulin human.

- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Basal”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Basal looks like and contents of the pack
After mixing, Insuman Basal is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Basal is supplied in vials containing 10 ml suspension (400 IU). Packs of 1 and 5 vials of 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Ísland
Vistor hf.
Sími: +354 535 7000

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Basal").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Basal").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,

- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Basal").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Basal 100 IU/ml suspension for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Basal is and what it is used for

Insuman Basal contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Basal is an insulin preparation with a gradual onset and long duration of action. The insulin is present as tiny crystals of insulin protamine.

Insuman Basal is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Basal

Do not use Insuman Basal

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Basal in cartridges is only suitable for injecting just under the skin using a reusable pen (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Basal.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Basal). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Basal

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Basal with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Basal in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Basal

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Basal

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Basal per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Basal.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Basal is injected under the skin 45 to 60 minutes before a meal.

Method of administration

Insuman Basal is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Basal into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the cartridges

Insuman Basal in cartridges is only suitable for injecting just under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.
To ensure you get the accurate dose, the Insuman Basal cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- ClikSTAR, Tactipen, Autopen 24, AllStar or AllStar PRO which deliver doses in steps of 1 unit.
Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer’s instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen. Mix the insulin well and check it before you insert it into the pen. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the cartridge or pen (with the cartridge in it) back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge. A new cartridge with a uniform suspension on mixing must then be used.

Always use a new cartridge if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

- Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If you use more Insuman Basal than you should
- If you **have injected too much Insuman Basal**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Basal
- If you **have missed a dose of Insuman Basal** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Basal
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Basal without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Basal and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Basal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insuman Basal next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Basal contains
- The active substance is insulin human. One ml of Insuman Basal contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insuman Basal"), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Basal looks like and contents of the pack
After mixing, Insuman Basal is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Basal is supplied in cartridges containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Basal").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Basal").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,

- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Basal").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Basal SoloStar 100 IU/ml suspension for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully including the Instructions for Use of Insuman Basal SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Basal is and what it is used for

Insuman Basal contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Basal is an insulin preparation with a gradual onset and long duration of action. The insulin is present as tiny crystals of insulin protamine. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insuman Basal is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Basal

Do not use Insuman Basal

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Basal in pre-filled pen is only suitable for injecting just under the skin (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Basal.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Basal). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Basal

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Basal with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Basal in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Basal

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Basal

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Basal per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Basal.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Basal is injected under the skin 45 to 60 minutes before a meal.

Method of administration

Insuman Basal is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Basal into a vein (blood vessel).

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing insulin human. Insuman Basal in pre-filled pen is only suitable for injecting just under the skin. Speak to your doctor if you need to inject your insulin by another method.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.

A safety test must be performed before each injection.

Mix the insulin well and check it before first use. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the pen back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or

on the sides or bottom of the cartridge in the pen. A new pen with a uniform suspension on mixing must then be used.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insuman Basal SoloStar, pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly, it has to be discarded and a new SoloStar has to be used.

If you use more Insuman Basal than you should
- If you **have injected too much Insuman Basal**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Basal
- If you **have missed a dose of Insuman Basal** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Basal
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Basal without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Basal and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Basal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Basal contains
- The active substance is insulin human. One ml of Insuman Basal contains 100 IU (International Units) of the active substance insulin human.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Basal), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Basal looks like and contents of the pack
After mixing, Insuman Basal is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Basal is supplied in pre-filled pens, SoloStar, containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Basal").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Basal").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Basal").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insuman Basal SoloStar suspension for injection in a pre-filled pen. Instructions for Use.

SoloStar is a prefilled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

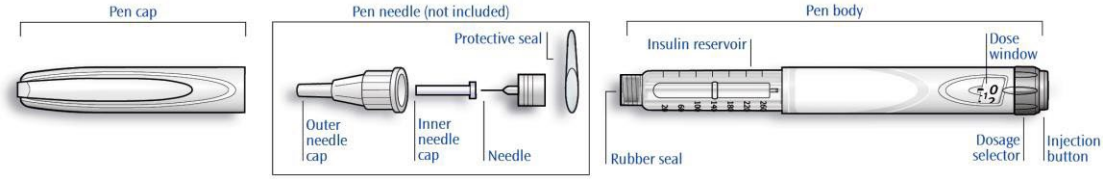
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or contact the local representative of the Marketing Authorization Holder mentioned on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

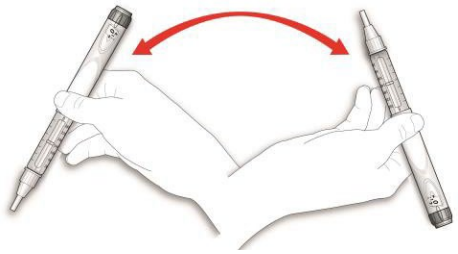
- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. Insuman SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insuman insulin used. The pictures below are for illustrative purposes only.

B. Take off the pen cap.

C. Check the appearance of your insulin.
If you are using a suspension insulin (Insuman Basal or Insuman mixtures), turn the pen up and down at least 10 times to resuspend the insulin. Turn the pen gently to avoid foaming in the cartridge.



After mixing check the appearance of your insulin. Insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

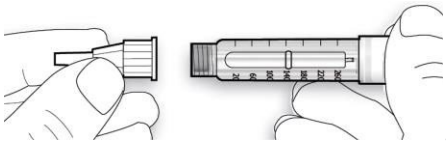
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of the needle, carefully read the "Instructions for Use" accompanying the needles.

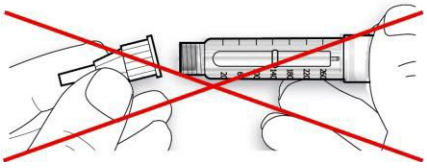
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



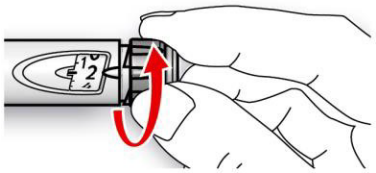
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



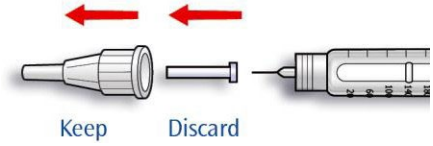
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



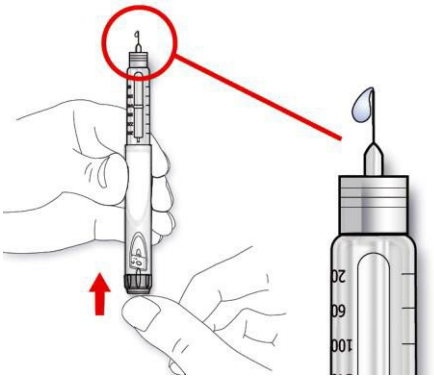
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

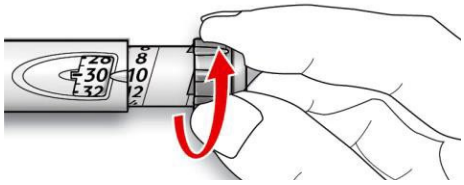
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows “0” following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



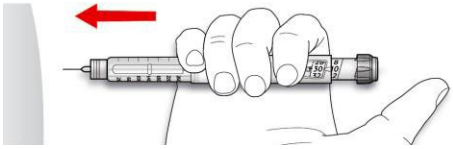
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

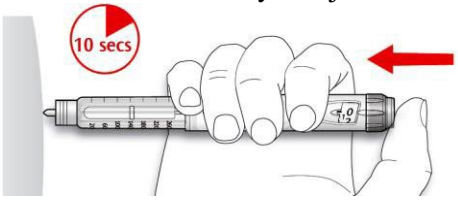
Step 5. Inject the dose

A. Use the injection method as instructed by your doctor, pharmacist or nurse.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin has been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:
- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up at room temperature. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet:Information for the user

Insuman Comb 15 100 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 15 is and what it is used for

Insuman Comb 15 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 15 is an insulin preparation with a gradual onset and long duration of action.

Insuman Comb 15 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 15

Do not use Insuman Comb 15

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Comb 15.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 15). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb°15

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 15 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 15 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 15

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 15

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 15 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 15.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 15 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insuman Comb 15 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 15 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the vials

Insuman Comb 15 contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Comb 15 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insuman Comb 15. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Comb 15 than you should
- If you **have injected too much Insuman Comb 15**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 15
- If you **have missed a dose of Insuman Comb 15** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 15
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 15 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 15 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reporting with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reporting with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 15

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insuman Comb 15 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 15 contains
- The active substance is insulin human. One ml of Insuman Comb 15 contains 100 IU (International Units) of the active substance insulin human. 15% of the insulin is dissolved in water; the other 85% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Comb°15), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 15 looks like and contents of the pack
After mixing, Insuman Comb 15 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 15 is supplied in vials containing 5 ml suspension (500 IU). Packs of 1 and 5 vials of 5 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb°15").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb°15").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),

- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb°15").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Comb 15 100 IU/ml suspension for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 15 is and what it is used for

Insuman Comb 15 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 15 is an insulin preparation with a gradual onset and long duration of action.

Insuman Comb 15 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 15

Do not use Insuman Comb 15

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Comb 15 in cartridges is only suitable for injecting just under the skin using a reusable pen (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Comb 15.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 15). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 15

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 15 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 15 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 15

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 15

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 15 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 15.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 15 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insuman Comb 15 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 15 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the cartridges

Insuman Comb 15 in cartridges is only suitable for injecting just under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.
To ensure you get the accurate dose, the Insuman Comb 15 cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- ClikSTAR, Tactipen, Autopen 24, AllStar or AllStar PRO which deliver doses in steps of 1 unit.
Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer’s instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen. Mix the insulin well and check it before you insert it into the pen. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the cartridge or pen (with the cartridge in it) back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge. A new cartridge with a uniform suspension on mixing must then be used.

Always use a new cartridge if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If you use more Insuman Comb 15 than you should
- If you **have injected too much Insuman Comb 15**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 15
- If you **have missed a dose of Insuman Comb 15** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 15
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 15 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 15 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 15

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after “EXP”. The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insuman Comb 15 next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 15 contains
- The active substance is insulin human. One ml of Insuman Comb 15 contains 100 IU (International Units) of the active substance insulin human. 15% of the insulin is dissolved in water; the other 85% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Comb 15”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 15 looks like and contents of the pack
After mixing, Insuman Comb 15 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 15 is supplied in cartridges containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

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Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 15").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 15").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,

- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 15").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage.Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Comb 15 SoloStar 100 IU/ml suspension for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully including the Instructions for Use of Insuman Comb 15 SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 15 is and what it is used for

Insuman Comb 15 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 15 is an insulin preparation with a gradual onset and long duration of action. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insuman Comb 15 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 15

Do not use Insuman Comb 15

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Comb 15 in pre-filled pen is only suitable for injecting just under the skin (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Comb 15.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups

If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 15). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 15

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),

- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 15 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 15 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 15

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 15

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 15 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 15.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 15 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insuman Comb 15 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 15 into a vein (blood vessel).

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing insulin human. Insuman Comb 15 in pre-filled pen is only suitable for injecting just under the skin. Speak to your doctor if you need to inject your insulin by another method.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.

A safety test must be performed before each injection.

Mix the insulin well and check it before first use. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the pen back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge in the pen. A new pen with a uniform suspension on mixing must then be used.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insuman Comb 15 SoloStar, pre-filled pen, SoloStar, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly, it has to be discarded and a new SoloStar has to be used.

If you use more Insuman Comb 15 than you should
- If you **have injected too much Insuman Comb 15**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 15
- If you **have missed a dose of Insuman Comb 15** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 15

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 15 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 15 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body),

severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effectsreported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 15

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after “EXP”. The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 15 contains

- The active substance is insulin human. One ml of Insuman Comb 15 contains 100 IU (International Units) of the active substance insulin human. 15% of the insulin is dissolved in water; the other 85% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insuman Comb 15"), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 15 looks like and contents of the pack

After mixing, Insuman Comb 15 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 15 is supplied in pre-filled pens, SoloStar, containing 3 ml suspension, (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

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Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb°15").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 15").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb°15").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insuman Comb 15 SoloStar suspension for injection in a pre-filled pen. Instructions for Use.

SoloStar is a pre-filled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

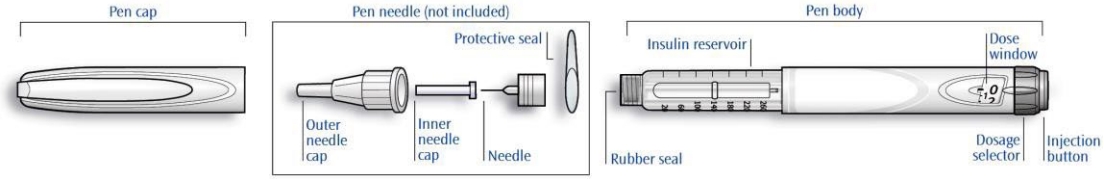
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or contact the local representative of the Marketing Authorization Holder mentioned on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

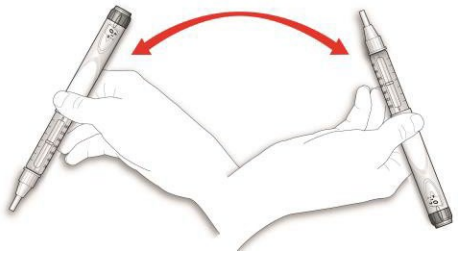
- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. Insuman SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insuman insulin used. The pictures below are for illustrative purposes only.

B. Take off the pen cap.

C. Check the appearance of your insulin.
If you are using a suspension insulin (Insuman Basal or Insuman mixtures), turn the pen up and down at least 10 times to resuspend the insulin. Turn the pen gently to avoid foaming in the cartridge.



After mixing check the appearance of your insulin. Insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

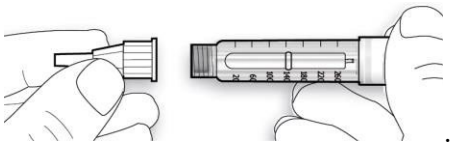
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of the needle, carefully read the “Instructions for Use” accompanying the needles.

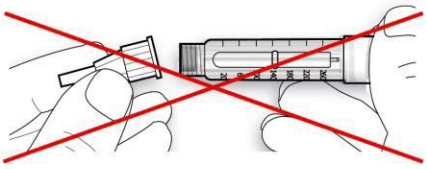
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



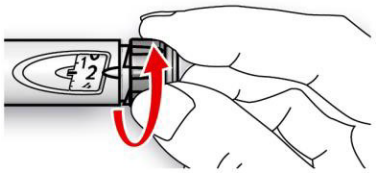
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



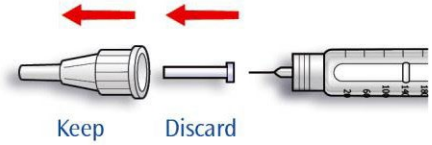
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



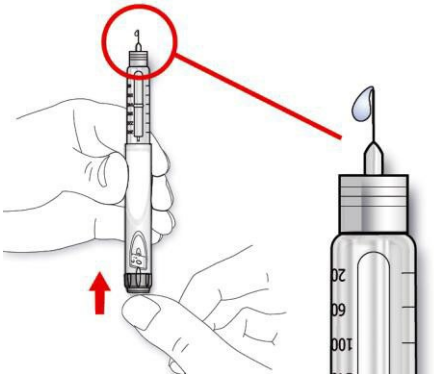
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

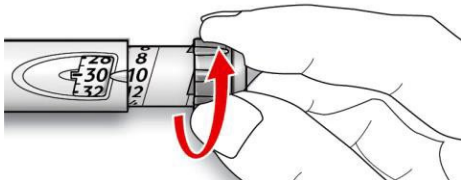
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



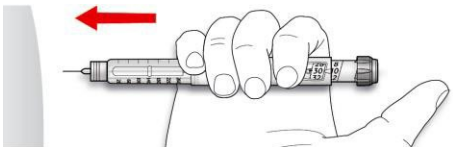
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

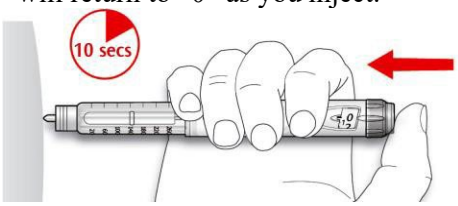
Step 5. Inject the dose

A. Use the injection method as instructed by your doctor, pharmacist or nurse.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin has been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:

- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up at room temperature. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet Information for the user

Insuman Comb 25 100 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 25 is and what it is used for

Insuman Comb 25 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 25 is an insulin preparation with a gradual onset and long duration of action.

Insuman Comb 25 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 25

Do not use Insuman Comb 25

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Comb 25.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 25). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 25

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 25 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 25 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 25

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb°25

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 25 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 25.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 25 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insuman Comb 25 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 25 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the vials

Insuman Comb 25 contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Comb 25 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insuman Comb 25. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Comb 25 than you should
- If you **have injected too much Insuman Comb 25**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 25
- If you **have missed a dose of Insuman Comb 25** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 25
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 25 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 25 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 25

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Comb 25 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 25 contains
- The active substance is insulin human. One ml of Insuman Comb 25 contains 100 IU (International Units) of the active substance insulin human. 25% of the insulin is dissolved in water; the other 75% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insuman Comb 25"), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 25 looks like and contents of the pack
After mixing, Insuman Comb 25 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 25 is supplied in vials containing 5 ml suspension (500 IU). Packs of 1 and 5 vials of 5 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Comb 25 40 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 25 is and what it is used for

Insuman Comb 25 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 25 is an insulin preparation with a gradual onset and long duration of action.

Insuman Comb 25 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 25

Do not use Insuman Comb 25

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Comb 25.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 25). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 25

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 25 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 25 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 25

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 25

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 25 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 25.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 25 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insuman Comb 25 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 25 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the vials

Insuman Comb 25 contains 40 IU insulin per ml. Only injection syringes designed for this insulin concentration (40 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Comb 25 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insuman Comb 25. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Comb 25 than you should
- If you **have injected too much Insuman Comb 25**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 25
- If you **have missed a dose of Insuman Comb 25** or if you **have not injected enough insulin,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 25
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 25 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 25 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 25

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after “EXP”. The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insuman Comb 25 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 25 contains
- The active substance is insulin human. One ml of Insuman Comb 25 contains 40 IU (International Units) of the active substance insulin human. 25% of the insulin is dissolved in water; the other 75% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Comb 25”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 25 looks like and contents of the pack
After mixing, Insuman Comb 25 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 25 is supplied in vials containing 10 ml suspension (400 IU). Packs of 1 and 5 vials of 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),

- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Comb 25 100 IU/ml suspension for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 25 is and what it is used for

Insuman Comb 25 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 25 is an insulin preparation with a gradual onset and long duration of action.

Insuman Comb 25 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 25

Do not use Insuman Comb 25

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Comb 25 in cartridges is only suitable for injecting just under the skin using a reusable pen (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Comb 25.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 25). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 25

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 25 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 25 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 25

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

3. How to use Insuman Comb 25

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 25 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 25.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 25 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insuman Comb 25 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 25 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the cartridges

Insuman Comb 25 in cartridges is only suitable for injecting just under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.
To ensure you get the accurate dose, the Insuman Comb 25 cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- ClikSTAR, Tactipen, Autopen 24, AllStar or AllStar PRO which deliver doses in steps of 1 unit.

Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen. Mix the insulin well and check it before you insert it into the pen. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the cartridge or pen (with the cartridge in it) back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge. A new cartridge with a uniform suspension on mixing must then be used.

Always use a new cartridge if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If you use more Insuman Comb 25 than you should
- If you **have injected too much Insuman Comb 25**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 25
- If you **have missed a dose of Insuman Comb 25** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 25
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 25 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 25 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may

cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 25

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Comb 25 next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 25 contains
- The active substance is insulin human. One ml of Insuman Comb 25 contains 100 IU (International Units) of the active substance insulin human. 25% of the insulin is dissolved in water; the other 75% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Comb 25”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 25 looks like and contents of the pack
After mixing, Insuman Comb 25 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 25 is supplied in cartridge containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

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Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.

Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.
-

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Comb 25 SoloStar 100 IU/ml suspension for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully including the Instructions for Use of Insuman Comb 25 SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 25 is and what it is used for

Insuman Comb 25 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 25 is an insulin preparation with a gradual onset and long duration of action. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insuman Comb 25 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 25

Do not use Insuman Comb 25

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Comb 25 in pre-filled pen is only suitable for injecting just under the skin (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Comb 25.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor

Special patient groups

If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 25). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling,-consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 25

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),

- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 25 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 25 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 25

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 25

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 25 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 25.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 25 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insuman Comb 25 is a fluid (suspension) for injection under the skin

Do NOT inject Insuman Comb 25 into a vein (blood vessel).

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing insulin human. Insuman Comb 25 in pre-filled pen is only suitable for injecting just under the skin. Speak to your doctor if you need to inject your insulin by another method.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.

A safety test must be performed before each injection.

Mix the insulin well and check it before first use. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the pen back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge in the pen. A new pen with a uniform suspension on mixing must then be used.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insuman Comb 25 SoloStar, pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly, it has to be discarded and a new SoloStar has to be used.

If you use more Insuman Comb 25 than you should
- If you **have injected too much Insuman Comb 25**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 25
- If you **have missed a dose of Insuman Comb 25** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 25
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 25 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 25 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body),

severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 25

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after “EXP”. The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 25 contains

- The active substance is insulin human. One ml of Insuman Comb 25 contains 100 IU (International Units) of the active substance insulin human. 25% of the insulin is dissolved in water; the other 75% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insuman Comb 25"), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 25 looks like and contents of the pack

After mixing, Insuman Comb 25 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 25 is supplied in pre-filled pens, SoloStar, containing 3 ml suspension, (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 25").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insuman Comb 25 SoloStar suspension for injection in a pre-filled pen. Instructions for Use.

SoloStar is a prefilled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

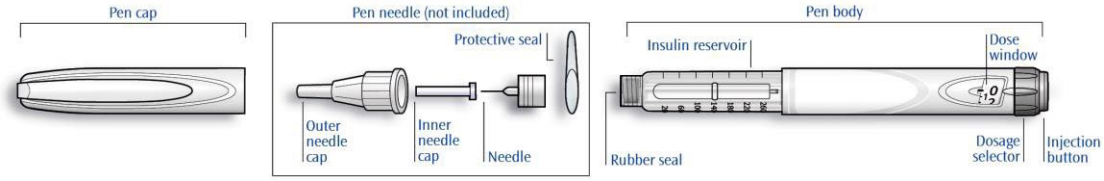
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or contact the local representative of the Marketing Authorization Holder mentioned on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

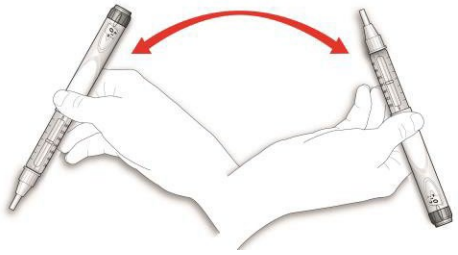
- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. Insuman SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insuman insulin used. The pictures below are for illustrative purposes only.

B. Take off the pen cap.

C. Check the appearance of your insulin.
If you are using a suspension insulin (Insuman Basal or Insuman mixtures), turn the pen up and down at least 10 times to resuspend the insulin. Turn the pen gently to avoid foaming in the cartridge.



After mixing check the appearance of your insulin. Insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

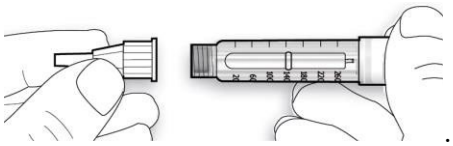
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of the needle, carefully read the “Instructions for Use” accompanying the needles.

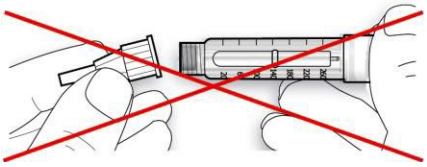
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



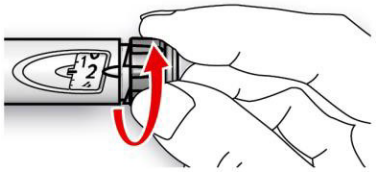
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



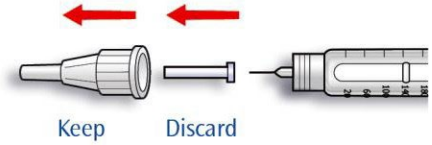
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



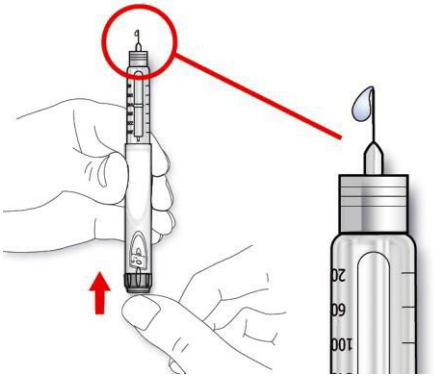
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

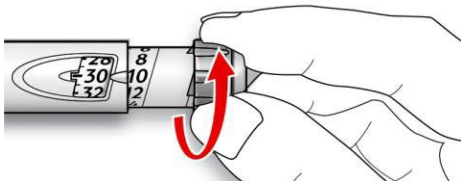
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows “0” following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



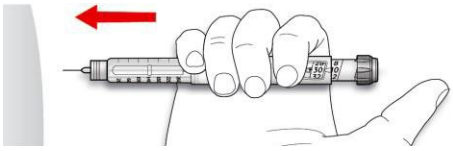
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

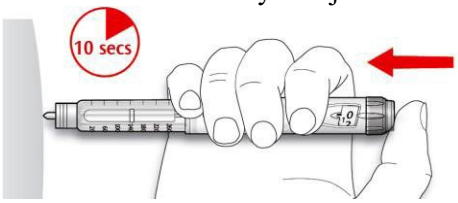
Step 5. Inject the dose

A. Use the injection method as instructed by your doctor, pharmacist or nurse.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin has been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:

- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up to room temperature. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet: Information for the user

Insuman Comb 30 100 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 30 is and what it is used for

Insuman Comb 30 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 30 is an insulin preparation with a gradual onset and long duration of action.

Insuman Comb 30 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 30

Do not use Insuman Comb 30

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Comb 30.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 30). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 30

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 30 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 30 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 30

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 30

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 30 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 30.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 30 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insuman Comb 30 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 30 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the vials

Insuman Comb 30 contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Comb 30 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insuman Comb 30. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Comb 30 than you should
- If you **have injected too much Insuman Comb 30**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 30
- If you **have missed a dose of Insuman Comb 30** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 30
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 30 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 30 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 30

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Comb 30 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 30 contains
- The active substance is insulin human. One ml of Insuman Comb 30 contains 100 IU (International Units) of the active substance insulin human. 30% of the insulin is dissolved in water; the other 70% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Comb 30”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 30 looks like and contents of the pack
After mixing, Insuman Comb 30 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 30 is supplied in vials containing 5 ml of suspension for injection (equivalent to 500 IU) or 10 ml of suspension for injection (equivalent to 1000 IU). Packs of 1 and 5 vials of 5 ml or 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

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Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 30").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 30").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,

- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 30").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Comb 30 100 IU/ml suspension for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 30 is and what it is used for

Insuman Comb 30 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 30 is an insulin preparation with a gradual onset and long duration of action.

Insuman Comb 30 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 30

Do not use Insuman Comb 30

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Comb 30 in cartridges is only suitable for injecting just under the skin using a reusable pen (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Comb 30.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 30). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 30

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 30 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 30 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 30

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 30

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 30 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 30.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 30 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insuman Comb 30 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 30 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps - special insulin preparations are available for use in such devices.

How to handle the cartridges

Insuman Comb 30 in cartridges is only suitable for injecting just under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.
To ensure you get the accurate dose, the Insuman Comb 30 cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- ClikSTAR, Tactipen, Autopen 24, AllStar or AllStar PRO which deliver doses in steps of 1 unit.
Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer’s instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen. Mix the insulin well and check it before you insert it into the pen. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the cartridge or pen (with the cartridge in it) back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge. A new cartridge with a uniform suspension on mixing must then be used.

Always use a new cartridge if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If you use more Insuman Comb 30 than you should
- If you **have injected too much Insuman Comb 30**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 30
- If you **have missed a dose of Insuman Comb 30** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 30
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 30 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 30 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body),

severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 30

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Comb 30 next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 30 contains

- The active substance is insulin human. One ml of Insuman Comb 30 contains 100 IU (International Units) of the active substance insulin human. 30% of the insulin is dissolved in water; the other 70% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Comb 30”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 30 looks like and contents of the pack

After mixing, Insuman Comb 30 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 30 is supplied in cartridge containing 3 ml suspension (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}
Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 30").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 30").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 30").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Comb 30 SoloStar 100 IU/ml suspension for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully including the Instructions for Use of Insuman Comb 30 SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor,pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 30 is and what it is used for

Insuman Comb 30 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 30 is an insulin preparation with a gradual onset and long duration of action. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insuman Comb 30 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 30

Do not use Insuman Comb 30

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Comb 30 in pre-filled pen is only suitable for injecting just under the skin (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Comb 30.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups

If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 30). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling,-consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 30

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),

- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 30 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 30 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 30

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 30

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 30 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 30.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 30 is injected under the skin 30 to 45 minutes before a meal.

Method of administration

Insuman Comb 30 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 30 into a vein (blood vessel).

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing insulin human. Insuman Comb 30 in pre-filled pen is only suitable for injecting just under the skin. Speak to your doctor if you need to inject your insulin by another method.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.

A safety test must be performed before each injection.

Mix the insulin well and check it before first use. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the pen back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge in the pen. A new pen with a uniform suspension on mixing must then be used.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insuman Comb 30 SoloStar, pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly, it has to be discarded and a new SoloStar has to be used.

If you use more Insuman Comb 30 than you should
- If you **have injected too much Insuman Comb 30**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 30
- If you **have missed a dose of Insuman Comb 30** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 30
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 30 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 30 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body),

severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 30

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after “EXP”. The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 30 contains

- The active substance is insulin human. One ml of Insuman Comb 30 contains 100 IU (International Units) of the active substance insulin human. 30% of the insulin is dissolved in water; the other 70% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Comb 30”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb30 looks like and contents of the pack

After mixing, Insuman Comb 30 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 30 is supplied in pre-filled pens, SoloStar, containing 3 ml suspension, (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 30").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 30").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 30").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

2. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insuman Comb 30 SoloStar suspension for injection in a pre-filled pen. Instructions for Use.

SoloStar is a pre-filled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

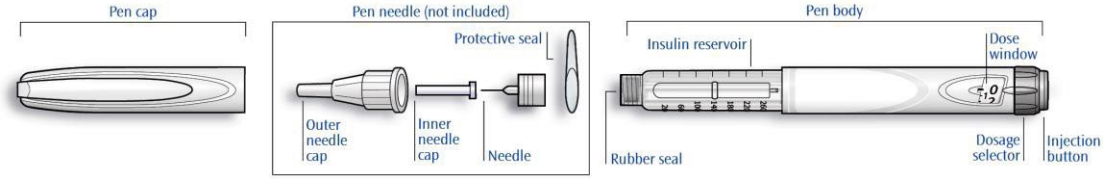
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or contact the local representative of the Marketing Authorization Holder mentioned on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

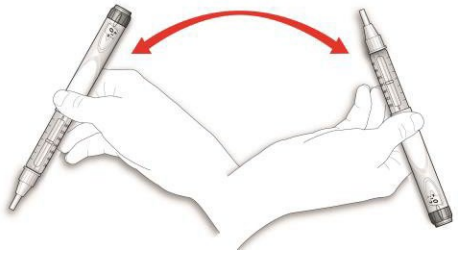
- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

Step 1. Check the insulin

A Check the label on your SoloStar to make sure you have the correct insulin. Insuman SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insuman insulin used. The pictures below are for illustrative purposes only.

B Take off the pen cap.

C Check the appearance of your insulin.
If you are using a suspension insulin (Insuman Basal or Insuman mixtures), turn the pen up and down at least 10 times to resuspend the insulin. Turn the pen gently to avoid foaming in the cartridge.



After mixing check the appearance of your insulin. Insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

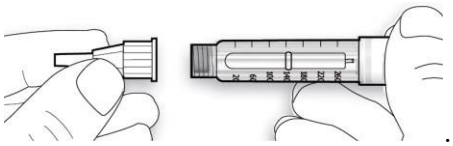
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of the needle, carefully read the “Instructions for Use” accompanying the needles.

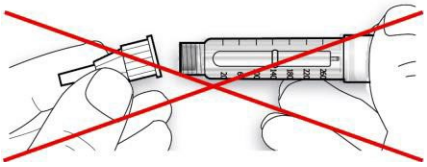
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



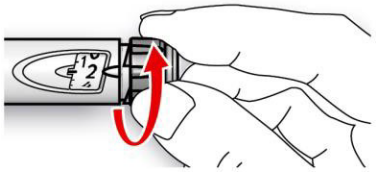
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



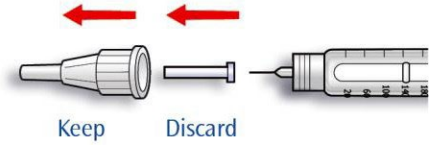
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A Select a dose of 2 units by turning the dosage selector.



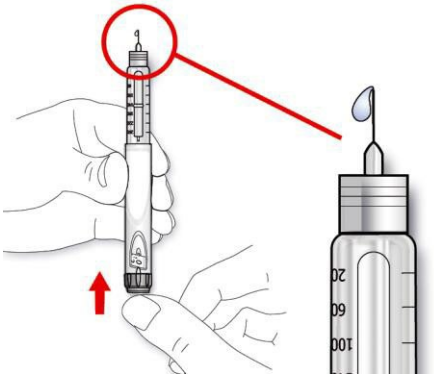
B Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C Hold the pen with the needle pointing upwards.

D Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

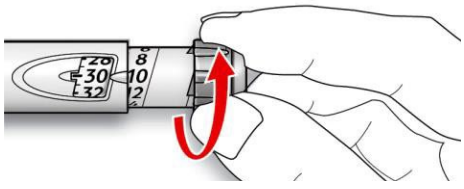
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A Check that the dose window shows “0” following the safety test.

B Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



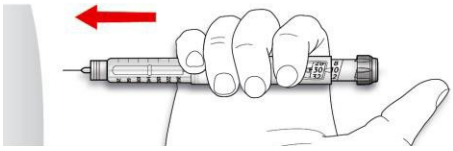
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

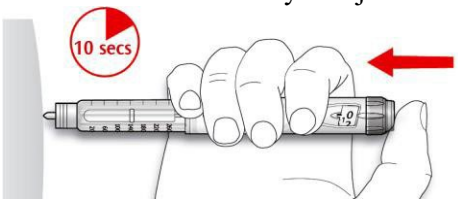
Step 5. Inject the dose

A Use the injection method as instructed by your doctor, pharmacist or nurse.

B Insert the needle into the skin.



C Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin has been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:

- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B Dispose of the needle safely.

C Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up to room temperature. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet: Information for the user

Insuman Comb 50 100 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 50 is and what it is used for

Insuman Comb 50 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 50 is an insulin preparation with a rapid onset and moderately long duration of action.

Insuman Comb 50 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 50

Do not use Insuman Comb 50

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Comb 50.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 50). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 50

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 50 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 50 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 50

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 50

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 50 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 50.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 50 is injected under the skin 20 to 30 minutes before a meal.

Method of administration

Insuman Comb 50 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 50 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the vials

Insuman Comb 50 contains 100 IU insulin per ml. Only injection syringes designed for this insulin concentration (100 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Comb 50 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insuman Comb 50. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Comb 50 than you should
- If you **have injected too much Insuman Comb 50**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 50
- If you **have missed a dose of Insuman Comb 50** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 50
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 50 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 50 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 50

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Comb 50 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 50 contains
- The active substance is insulin human. One ml of Insuman Comb 50 contains 100 IU (International Units) of the active substance insulin human. 50% of the insulin is dissolved in water; the other 50% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Comb 50”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 50 looks like and contents of the pack
After mixing, Insuman Comb 50 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 50 is supplied in vials containing 5 ml suspension (500 IU). Packs of 1 and 5 vials of 5 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

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Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,

- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Comb 50 40 IU/ml suspension for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 50 is and what it is used for
Insuman Comb 50 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 50 is an insulin preparation with a rapid onset and moderately long duration of action.

Insuman Comb 50 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

1. What you need to know before you use Insuman Comb 50

Do not use Insuman Comb 50

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Comb 50.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 50). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 50

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),

- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 50 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 50 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 50

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 50

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 50 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 50.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 50 is injected under the skin 20 to 30 minutes before a meal.

Method of administration

Insuman Comb 50 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 50 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the vials

Insuman Comb 50 contains 40 IU insulin per ml. Only injection syringes designed for this insulin concentration (40 IU per ml) must be used. The injection syringes must not contain any other medicines or traces of medicines (such as traces of heparin).

Before the first withdrawal of insulin you must remove the safety tear-off lid on the vial.

Mix the insulin well immediately before each injection. This is best done by rolling the vial tilted between the palms of the hands. Do not shake the vial vigorously as this could damage the insulin and cause froth to form. Froth can make it difficult for you to measure the correct dose.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the vial. A new vial with a uniform suspension on mixing must then be used.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin. Do not mix insulin with any other medicines except with insulin human preparations as detailed below.

Insuman Comb 50 may be mixed with all insulin human preparations, EXCEPT those specially designed for use in insulin pumps. Also, it must NOT be mixed with animal source insulins or insulin analogues.

Your doctor will tell you if you have to mix insulin human preparations. If you need to inject a mixture, draw the other insulin into the injection syringe before Insuman Comb 50. Inject as soon as you have mixed them. Do not mix insulins of different strengths (for example 100 IU per ml and 40 IU per ml).

If you use more Insuman Comb 50 than you should
- If you **have injected too much Insuman Comb 50**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 50
- If you **have missed a dose of Insuman Comb 50** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 50
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 50 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 50 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 50

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put Insuman Comb 50 next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 50 contains
- The active substance is insulin human. One ml of Insuman Comb 50 contains 40 IU (International Units) of the active substance insulin human. 50% of the insulin is dissolved in water; the other 50% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under "Important information about some of the ingredients of Insuman Comb 50"), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 50 looks like and contents of the pack
After mixing, Insuman Comb 50 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 50 is supplied in vials containing 10 ml suspension (400 IU). Packs of 1 and 5 vials of 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη AEBE
Τηλ: +30 210 900 16 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,

- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Comb 50 100 IU/ml suspension for injection in a cartridge
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 50 is and what it is used for

Insuman Comb 50 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 50 is an insulin preparation with a rapid onset and moderately long duration of action.

Insuman Comb 50 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 50

Do not use Insuman Comb 50

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Comb 50 in cartridges is only suitable for injecting just under the skin using a reusable pen (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Comb 50.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 50). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 50

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 50 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 50 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 50

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 50

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 50 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 50.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 50 is injected under the skin 20 to 30 minutes before a meal.

Method of administration

Insuman Comb 50 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 50 into a vein (blood vessel).

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

Do not use it in insulin pumps or other infusion pumps – special insulin preparations are available for use in such devices.

How to handle the cartridges

Insuman Comb 50 in cartridges is only suitable for injecting just under the skin using a reusable pen. Speak to your doctor if you need to inject your insulin by another method.
To ensure you get the accurate dose, the Insuman Comb 50 cartridges are to be used only with the following pens:
- JuniorSTAR which delivers doses in steps of 0.5 units
- ClikSTAR, Tactipen, Autopen 24, AllStar or AllStar PRO which deliver doses in steps of 1 unit.
Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer’s instructions for using the pen must be followed carefully for loading the cartridge, attaching the injection needle, and administering the insulin injection.

Keep the cartridge at room temperature for 1 or 2 hours before inserting it into the pen. Mix the insulin well and check it before you insert it into the pen. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the cartridge or pen (with the cartridge in it) back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge. A new cartridge with a uniform suspension on mixing must then be used.

Always use a new cartridge if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with your insulin, have it checked by your doctor or pharmacist.

Special care before injection

Before injection remove any air bubbles (see instructions for using the pen). Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.
- Do not re-fill and re-use empty cartridges.
- Do not add any other insulin to the cartridge.
- Do not mix insulin with any other medicines.

Problems with the pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If you use more Insuman Comb 50 than you should
- If you **have injected too much Insuman Comb 50**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 50
- If you **have missed a dose of Insuman Comb 50** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 50
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 50 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 50 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may

cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.

- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 50

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the cartridge after "EXP". The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Comb 50 next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges
Cartridges in-use (in the insulin pen) or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The cartridge in-use must not be stored in a refrigerator. Do not use the cartridge after this time period.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 50 contains
- The active substance is insulin human. One ml of Insuman Comb 50 contains 100 IU (International Units) of the active substance insulin human. 50% of the insulin is dissolved in water; the other 50% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Comb 50”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 50 looks like and contents of the pack
After mixing, Insuman Comb 50 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 50 is supplied in cartridge containing 3 ml suspension, (300 IU). Packs of 3, 4, 5, 6, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

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Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

Hypoglycaemia is also more likely to occur if:

- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Comb 50 Solostar 100 IU/ml suspension for injection in a pre-filled pen
Insulin human

Read all of this leaflet carefully including the Instructions for Use of Insuman Comb 50 SoloStar, pre-filled pen, before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Comb 50 is and what it is used for

Insuman Comb 50 contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Comb 50 is an insulin preparation with a rapid onset and moderately long duration of action. It comes in cartridges sealed in disposable pen injectors, SoloStar.

Insuman Comb 50 is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Comb 50

Do not use Insuman Comb 50

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Insuman Comb 50 in pre-filled pen is only suitable for injecting just under the skin (see also section 3). Speak to your doctor if you need to inject your insulin by another method.

Talk to your doctor, pharmacist or nurse before using Insuman Comb 50.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise), injection technique as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups

If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Comb 50). Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, needles etc.,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Comb 50

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),

- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Comb 50 with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Comb 50 in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Comb 50

This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Comb 50

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Comb 50 per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to inject a higher or lower dose of Insuman Comb 50.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Frequency of administration

Insuman Comb 50 is injected under the skin 20 to 30 minutes before a meal.

Method of administration

Insuman Comb 50 is a fluid (suspension) for injection under the skin.

Do NOT inject Insuman Comb 50 into a vein (blood vessel).

SoloStar delivers insulin in doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Your doctor will show you in which area of the skin you should inject your insulin. With each injection, change the puncture site within the particular area of skin that you are using.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing insulin human. Insuman Comb 50 in pre-filled pen is only suitable for injecting just under the skin. Speak to your doctor if you need to inject your insulin by another method.

Read carefully the "SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

A new injection needle must be attached before each use. Only use needles that have been approved for use with SoloStar.

A safety test must be performed before each injection.

Mix the insulin well and check it before first use. Later, you must mix the insulin well again immediately before each injection.

Mixing is best done by gently tilting the pen back and forth at least 10 times. To assist in mixing, three tiny metal balls are present in the cartridge.

After mixing, the suspension must have a uniform milky-white appearance. It must not be used if it remains clear or if, for example, clumps, flakes, particles or anything similar are in the suspension or on the sides or bottom of the cartridge in the pen. A new pen with a uniform suspension on mixing must then be used.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with SoloStar, consult your doctor, pharmacist or nurse.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Special care before injection

Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insuman Comb 50 SoloStar, pre-filled pen, is not designed to allow any other insulin to be mixed in the cartridge.

Empty pens must not be re-filled and must be properly discarded.

Do not use SoloStar if it is damaged or not working properly, it has to be discarded and a new SoloStar has to be used.

If you use more Insuman Comb 50 than you should
- If you **have injected too much Insuman Comb 50**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Comb 50
- If you **have missed a dose of Insuman Comb 50** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Comb 50
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Comb 50 without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Comb 50 and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body),

severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known
- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.
- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Comb 50

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after “EXP”. The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in-use or carried as a spare may be stored for a maximum of 4 weeks not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). The pen in-use must not be stored in a refrigerator. Do not use the pen after this time period.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Comb 50 contains
- The active substance is insulin human. One ml of Insuman Comb 50 contains 100 IU (International Units) of the active substance insulin human. 50% of the insulin is dissolved in water; the other 50% is present as tiny crystals of insulin protamine.
- The other ingredients are: protamine sulphate, metacresol, phenol, zinc chloride, sodium dihydrogen phosphate dihydrate, glycerol, sodium hydroxide (see section 2 under “Important information about some of the ingredients of Insuman Comb 50”), hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Comb 50 looks like and contents of the pack
After mixing, Insuman Comb 50 is a uniformly milky fluid (suspension for injection), with no clumps, particles or flocculation visible.

Insuman Comb 50 is supplied in pre-filled pens, SoloStar, containing 3 ml suspension, (300 IU). Packs of 3, 4, 5, 6, 9 and 10 pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

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Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pen does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Comb 50").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Insuman Comb 50 SoloStar suspension for injection in a pre-filled pen. Instructions for Use.

SoloStar is a pre-filled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.

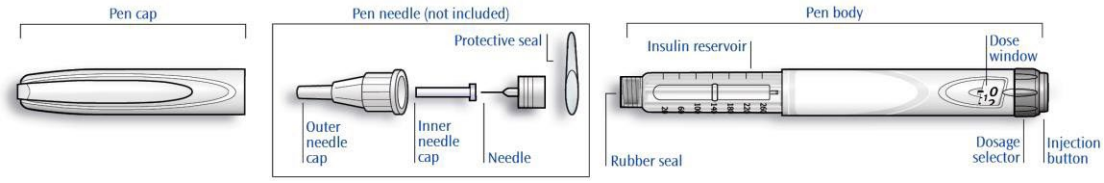
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use SoloStar to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your doctor, pharmacist or nurse or contact the local representative of the Marketing Authorization Holder mentioned on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

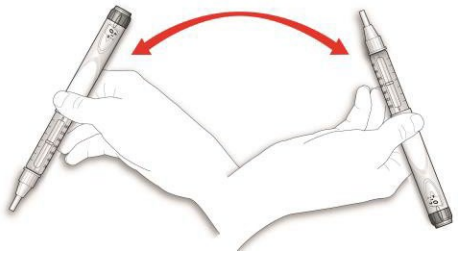
- Always attach a new needle before each use. Only use needles that have been approved for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. Insuman SoloStar is white with a colour on the injection button. The injection button colour will vary based on the formulation of Insuman insulin used. The pictures below are for illustrative purposes only.

B. Take off the pen cap.

C. Check the appearance of your insulin.
If you are using a suspension insulin (Insuman Basal or Insuman mixtures), turn the pen up and down at least 10 times to resuspend the insulin. Turn the pen gently to avoid foaming in the cartridge.



After mixing check the appearance of your insulin. Insulin suspensions must have an evenly milky-white appearance.

Step 2. Attach the needle

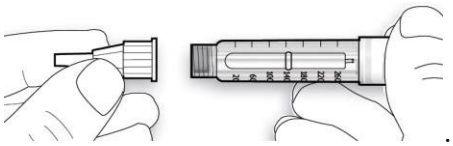
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of the needle, carefully read the “Instructions for Use” accompanying the needles.

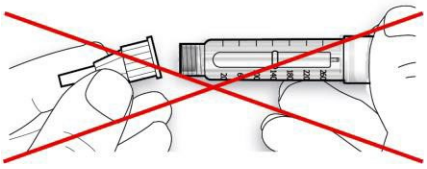
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



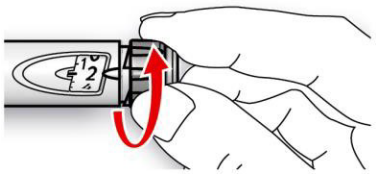
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



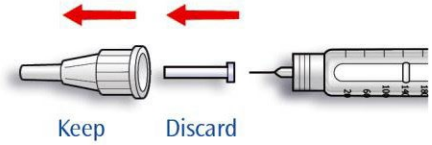
Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



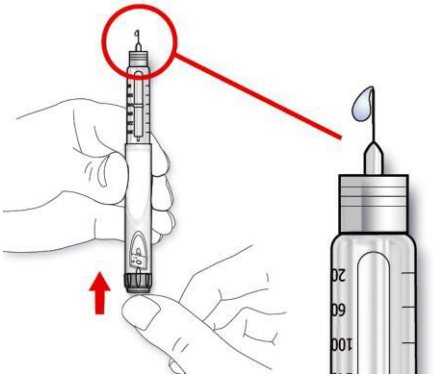
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

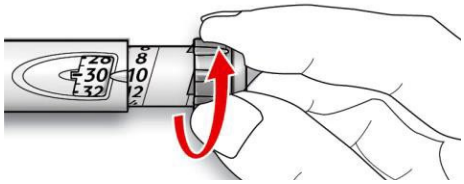
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



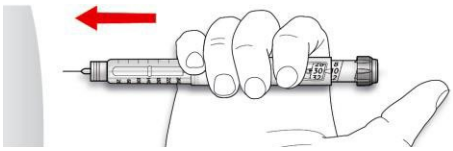
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

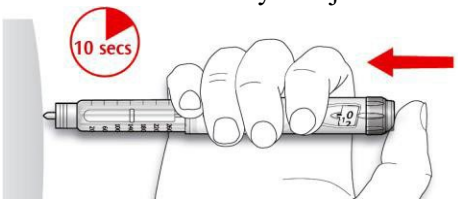
Step 5. Inject the dose

A. Use the injection method as instructed by your doctor, pharmacist or nurse.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin has been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:

- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle. Follow recommended safety measures for removal and disposal of needles (e.g. contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up to room temperature. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

Package leaflet: Information for the user

Insuman Infusat 100 IU/ml solution for injection in a vial
Insulin human

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Insuman Infusat is and what it is used for

Insuman Infusat contains the active substance insulin human which is made by a biotechnology process and is identical with the body's own insulin.

Insuman Infusat is an insulin preparation with a rapid onset and short duration of action.
Insuman Infusat must only be used in insulin pumps suitable for this insulin.

Insuman Infusat is used to reduce high blood sugar in patients with diabetes mellitus who need treatment with insulin. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. What you need to know before you use Insuman Infusat

Do not use Insuman Infusat

If you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Insuman Infusat.
Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Skin changes at the injection site
The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see How to use Insuman Infusat). Contact your doctor if

you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Travel
Before travelling, consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc.,
- correct storage of your insulin while travelling,
- whom to contact in the event of technical problems with your pump,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require a lot of care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Insuman Infusat

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),

- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Insuman Infusat with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby. However, there is no experience with the use of Insuman Infusat in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines). You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Insuman Infusat contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

3. How to use Insuman Infusat

Dose

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Infusat per day you will need, how much of this is infused continuously ("basal rate") and how much and when you need additional insulin as an "insulin boost" ("bolus dose"),
- tell you when to check your blood sugar level, and whether you need to carry out urine tests,
- tell you when you may need to use a higher or lower dose of Insuman Infusat,

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Method of administration

Insuman Infusat is a fluid (suspension) for injection under the skin.

Your doctor will show you how and in which area of the skin you should infuse your insulin and how often you must change the puncture site within the particular area of skin where you are infusing the insulin. Speak to your doctor before you change the area of skin that you are infusing.

Do not use Insuman Infusat in peristaltic pumps with silicone tubing. Situations in which you must not start or continue to use insulin pumps are described in the operating manuals for these pumps.

How to handle the vials

Insuman Infusat must only be used in insulin pumps suitable for this insulin. Only tetrafluoroethylene or polyethylene catheters must be used for infusion. The operating manual provided with the pump will tell you how to use it.

Insuman Infusat must only be used if the solution is clear, colourless, with no solid particles visible, and has a water-like consistency.

Special care before injection

Before starting the infusion remove any air bubbles. Make sure that neither alcohol nor other disinfectants or other substances contaminate the insulin.

Do not mix insulin with any other medicines. Insuman Infusat must NOT be mixed with any other insulin preparations.

Insulin pump faults

You should always consider the possibility of a technical problem if, in order to achieve the desired blood sugar levels,
- you need additional insulin ("bolus doses") at larger doses or more often than usual, or
- you need additional insulin ("bolus doses") at smaller doses or less often than usual.

For details on safety precautions in the use of insulin pumps see the operating manual.

If the pump does not function well, you can draw the insulin from the cartridge into an injection syringe. Therefore, keep injection syringes and injection needles as well. However, use only those

injection syringes which are designed for an insulin concentration of 100 IU (International Units) per ml.

If you use more Insuman Infusat than you should
- If you **have injected too much Insuman Infusat**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Insuman Infusat
- If you **have missed a dose of Insuman Infusat** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Insuman Infusat
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Infusat without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Insuman Infusat and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most serious side effects
Side effects reported uncommonly (may affect up to 1 in 100 people)
- **Severe allergic reaction with low blood pressure** (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- The most frequent side effect is **hypoglycaemia (low blood sugar)**. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar or high blood sugar, see the box at the end of this leaflet.
- **Severe allergic reactions** to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.
- Injection site reactions

Side effects reported uncommonly
- Injection site urticaria (itchy rash)

Side effects reported with a frequency not known

- Sodium retention
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.

- Skin changes at the injection site

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink (lipoatrophy) or thicken (lipohypertrophy). Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis). The insulin may not work very well if you inject into a lumpy area. Change the injection site with each injection to help prevent these skin changes.

- Skin and allergic reactions

Other mild reactions at the injection site (such as injection site redness, unusually intense pain on injection site, itching, injection site swelling or injection site inflammation) may occur. They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

- Insulin antibodies

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Infusat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

Unopened vials

Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Infusat next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials

Once in-use, the vial may be stored for a maximum of 4 weeks in the outer carton not above 25°C and away from direct heat (for example next to a heating unit) or direct light (direct sunlight or next to a lamp). Do not use the vial after this time period. It is recommended that the date of the first use be noted on the label.

Once in the pump, Insuman Infusat may be kept for up to 2 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Insuman Infusat contains

- The active substance is insulin human. One ml of Insuman Infusat contains 100 IU (International Units) of the active substance insulin human.

- The other ingredients are: phenol, zinc chloride, trometamol, poloxamer 171, glycerol, sodium hydroxide, hydrochloric acid (for pH adjustment) and water for injections.

What Insuman Infusat looks like and contents of the pack
Insuman Infusat is a clear, colourless solution for injection, with no solid particles visible, and of water-like consistency.
Insuman Infusat is supplied in vials contains 10 ml solution (1000 IU). Pack of 3 vials of 10 ml is available.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Nederland
Sanofi B.V..
Tel: +31 20 245 4000

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal

Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- your insulin pump does not work properly,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Infusat").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Infusat").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,

- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body
Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain
Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if
- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Infusat").

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Stop your insulin infusion (if necessary, by withdrawing the needle) at least until you feel that you are fully alert again. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Package leaflet: Information for the user

Insuman Implantable 400 IU/ml, solution for infusion
Insulin human

The package leaflet is available in your national language on the European Medicines Agency web site: http://www.ema.europa.eu/. Alternatively you can contact the Marketing Authorisation Holder listed at the end of this leaflet.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Insuman Implantable is and what it is used for

Insuman Implantable contains the active substance insulin human which is made by a biotechnology process and is identical to the body's own insulin.

Insuman Implantable is an insulin solution with a rapid onset and short duration of action. When used with an implantable insulin pump, Insuman Implantable will be continuously infused in your body and thus, may replace a long-acting insulin.

Insuman Implantable (400 IU/ml) contains 4 times as much insulin in 1 ml as standard insulin (100 IU/ml). This means that Insuman Implantable is more concentrated than standard insulin.

Insuman Implantable is used to reduce high blood sugar in adult patients with a certain form of diabetes (type 1 diabetes mellitus). These patients are not adequately controlled despite intensive injection of insulin under their skin (multiple daily injections or insulin pump therapy).
Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

Insuman Implantable must only be used in the Medtronic MiniMed pump which is implanted under the skin of your belly and infuses your insulin continuously.

2. What you need to know before you use Insuman Implantable

Do not use Insuman Implantable
- if you are allergic to insulin or any of the other ingredients of this medicine (listed in section 6).
- via other routes of administration (e.g. injection).

Do not use the Medtronic MiniMed Implantable Pump
- if you are allergic to titanium alloy, polysulfone or silicone materials used in the implanted components of the pump.
- with other insulin medicine other than Insuman Implantable.
- in adolescents who have not reached adult size.
- if you live permanently at heights above 2439 meters (8000 feet).

Warnings and precautions
If you are ill or have mental problems that make you unable to make changes to your pump based on your blood glucose level or to take the appropriate actions if you have a problem with your pump, talk to your doctor.

Before you can use the Medtronic MiniMed Implantable Pump, you will be trained. This training will be about this implantable insulin pump, how to use the pump and how to deal with special situations, such as hypoglycaemia or hyperglycaemia. In addition, you should read and follow the instructions given in the patient manual accompanying the Medtronic MiniMed Implantable Pump.
Do not use Insuman Implantable with any other syringes or pumps (external or implantable) than the implantable pump supplied by Medtronic MiniMed.

Follow closely the instructions for dose, monitoring (blood and/or urine tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

If you expect to have frequent medical imaging (e.g. MRI or ultrasound), talk to your doctor.

If you are allergic to this medicine or to animal insulins, talk to your doctor.

Hypoglycaemia
Low blood sugar levels (hypoglycaemia) may occur if you administer too much insulin.
If you experience severe low blood sugar levels, this may indicate a problem with your pump. If this happens, immediately contact your doctor who is trained to perform pump investigations.
You must closely monitor your blood sugar level on refill days. During a refill procedure, a very small amount of Insuman Implantable may be deposited subcutaneously, which might result in low blood sugar levels.

Hyperglycaemia
It is possible that the insulin can cause blockage of the implantable pump. You must check your blood sugar level at least four times daily to detect and prevent high blood sugar levels due to the pump not working properly. If you get severe hyperglycemia (very high blood sugar) or ketoacidosis (build up of acid in the blood because the body is breaking down fat instead of sugar) or coma, this may indicate a problem with the pump. If you notice a rapid increase in blood sugar level which does not respond to a bolus dose of insulin, contact your doctor immediately. She/he is trained to perform pump investigations. In case the pump does not work properly you must always have access to injection devices (e.g. syringe or pen) and insulin suitable for subcutaneous injection. To prevent such pump problems, your doctor will schedule appointments at least every 6-months to rinse your pump.

In case your pump is damaged or your Personal Pump Communicator (PPC) is damaged or lost, review with your doctor what you should do in case your pump does not work correctly.

Site of the pump implantation
Infection of the pump pocket (where your pump is placed), erosion of the skin where your pump is implanted and poor healing of the incision site in your skin can occur. If you notice pain, redness, swelling in the area of your pump, contact your doctor.

Liver reaction
Insulin administration via the pump can cause a fat infiltration of the liver at single, well-defined locations (called focal hepatic steatosis). This happens when the tip of your catheter is fixed or in very

close proximity to your liver. This seems to be reversible when your catheter is repositioned or your insulin infusion stopped and without consequences on your health (see section 4).

Antibodies to insulin
Insulin treatment by continuous infusion in the body is likely to cause your body to produce antibodies to insulin (substances that act against insulin). This may require a change to your insulin dose (see section 4).

Special patient groups
If you have liver or kidneys problems or if you are elderly, speak to your doctor as you may need a lower dose.

Travel
Talk to your doctor to find out what you should do if you plan:
- to live at a height above 2439 meters (8000 feet)
- to travel to a height above 2439 meters (8000 feet) other than commercial aircraft
- to dive below 7.6 meters (25 feet).

Before travelling, consult your doctor. You may need to talk about:
- the availability of your insulin and the hospital which will be able to replace the Insuman Implantable in the country you are visiting,
- whom to contact in the event of technical problems with your pump,
- timing of meals and insulin administration while travelling,
- the possible problems of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations if you feel unwell or become ill.

Illnesses and injuries
In the following situations, the management of your diabetes may require extra care (e.g. urine and blood tests):
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough, your blood sugar level may become too low (hypoglycaemia).

In most cases you will need to see a doctor. **Make sure that you contact a doctor quickly.**

Because you have type 1 diabetes, an insulin dependent diabetes mellitus, do not stop your insulin. If you stop using your insulin this could lead to a very high blood sugar level.
You must also make sure you get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Children and adolescents
There is no experience with Insuman Implantable in children and adolescents below 18 years. Due to the size of the pump, adolescents who have not reached the adult size must not be implanted.

Other medicines and Insuman Implantable
Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). You may need to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level, and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),

- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat the thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine). These medicines are used for mental problems that affect how you think, feel or act.

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or stop the first warning symptoms which help you to recognise hypoglycaemia.

If you are not sure whether you are taking one of those medicines, ask your doctor or nurse.

Insuman Implantable with alcohol
Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. There is no clinical information with the use of Insuman Implantable in an implantable pump in pregnant women.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Particularly careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines
Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels),
- you have problems with your sight.

Keep this in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines).

You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Insuman Implantable
This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

3. How to use Insuman Implantable

Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor or nurse if you are not sure.
Insuman Implantable will be prescribed by a doctor who has received training in the use of the Medtronic MiniMed Implantable Pump.

Dose
Based on your life-style and the results of your blood sugar (glucose) tests, your doctor will
- determine how much Insuman Implantable per day you will need,
- tell you when to check your blood sugar level, and whether you need to carry out urine tests.

Many things may affect your blood sugar level. You should know what these are so that you can react correctly to changes in your blood sugar level and prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

The insulin in your pump must be replaced every 40 to 45 days with new insulin. Do not extend this period of time. Contact your doctor immediately if you are unable to go to the hospital or clinicto replace the insulin in your pump. Based on your needs, you may need to replace your insulin earlier.

The pump is not connected to a glucose meter. You should practice good diabetes care and test your own blood sugar levels at least four times daily to check your blood sugar levels and determine insulin doses.

Part of the daily insulin dose is infused continuously by the Medtronic MiniMed Implantable Pump and the remaining part of the daily dose is administered by you, using the same pump, as a bolus before meals. The amount of insulin is constantly monitored through the PPC which communicates with the pump via radio waves.

Method of administration
Insuman Implantable must only be used in the Medtronic MiniMed implantable pump.
Insuman Implantable must not be used with any other type of injection devices (e.g. syringes).

The Medtronic MiniMed Implantable Pump, which is implanted under the skin of your belly, infuses your insulin continuously (continuous intraperitoneal infusion). You will be admitted to the hospital to have the Medtronic MiniMed Implantable Pump surgically implanted in your belly. The pump system will also be programmed and tested prior to your leaving the hospital.

All pump procedures (such as pump refill, rinsing of the pump, pump investigations to check whether your pump works properly) are performed using sterile technique to avoid risk of infection. Infections around the pump implantation site may require the removal of your pump (explantation of the pump).

<u>Pump refill</u>
How to handle the vials
Your doctor will be handling the insulin vials and has the accessories (e.g. refill syringes and needles) and equipment required to fill your implantable pump.

Refilling the pump is a sterile procedure which must be carried out in the hospital or clinic. The unused insulin in the pump will be removed and the pump refilled with fresh insulin.
The insulin in your pump must be replaced every 40 to 45 days with new insulin or earlier based on your insulin needs. Alarms in your PPC will let you know if your reservoir level is getting low. Do not extend this period of time (45 days) and contact your doctor immediately if you are unable to go to the hospital or clinic to replace the insulin in your pump.
You must closely monitor your blood sugar level on refill days. During this procedure, a very small amount of Insuman Implantable may be deposited under your skin, which may result in low blood sugar levels.

Pump blockage
Insulin deposits can cause blockage of the pump. If you need to increase your insulin to maintain your blood sugar level, if you experience refractory hyperglycaemia, this may indicate a problem with the pump. You must contact your doctor immediately. She/he is trained to perform pump procedures which are needed tomake sure your pump works properly. To prevent pump problems, your doctor will schedule appointments at least every 6-months to rinse your pump.

If you use more Insuman Implantable than you should
Your doctor will program maximum dose limits into your PPC.
If you try to deliver more than 2.5 times the bolus maximum in one hour, the alarm **"hourly max exceeded"** will be displayed on your PPC screen. If you need to deliver one additional bolus, press "**SEL**" and then "**ACT**". You may exceed this limit by programming only one bolus within 10 minutes. If you try to deliver a second bolus, you will receive the hourly max exceeded alarm on your PPC screen again.

If you forget to use Insuman Implantable
- If you forget the dose before a meal:

You may feel symptoms of high blood sugar after you eat. If this occurs, you should contact your doctor immediately. Your doctor will tell you how to manage your blood glucose levels.

- If you forget to have your pump refilled:

The insulin in your pump must be replaced every 40 to 45 days with new insulin. Do not extend this period of time (45 days) and contact your doctor immediately if you are unable to go to the hospital or clinic to replace the insulin in your pump.
Based on your needs, you may need to replace your insulin earlier. The PPC prompts you with messages on the screen. If your pump has run out of insulin or is delivering less insulin than you need, you may feel symptoms of high blood sugar. If this happens, contact your doctor immediately. Your doctor will tell you how to manage your blood glucose levels.

If you stop using Insuman Implantable
This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Insuman Implantable without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

► Side effects reported with the insulin

Most serious side effects
Side effects reported commonly (may affect up to 1 in 10 people)
- The most frequent side effect is **hypoglycaemia** (low blood sugar). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. For further information on the side effects of low blood sugar, see the box at the end of this leaflet.
- **Hyperglycaemia**: If your blood sugar is too high, you may experience hyperglycaemia.

Hyperglycaemia can become serious and lead to a serious condition (ketoacidosis). For further information on side effects of high blood sugar, see the box at the end of this leaflet.

Side effects reported uncommonly (may affect up to 1 in 100 people)
- Severe allergic reaction with low blood pressure (shock)

Side effects reported with a frequency not known (cannot be estimated from the available data)
- Severe allergic reactions to insulin may occur which may become life-threatening. Such reactions to insulin or to the excipients can cause large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating.

Other side effects
Side effects reported commonly
- Oedema

Insulin treatment may cause temporary build-up of water in the body with swelling in the calves and ankles.

Side effects reported with a frequency not known
- Sodium retention

Insulin may also cause sodium retention, particularly if previously poor metabolic control is improved by intensified insulin therapy
- Eye reactions

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.
- Insulin antibodies

Insulin administration via the intraperitoneal route can cause the body to produce antibodies to insulin (substances that act against insulin). Elevated levels of antibodies to insulin are not commonly associated with a need to change your insulin dose or occurrence of serious side effects.
- Liver reaction

Insulin administration via the pump can cause a fat infiltration of the liver at single, well-defined locations (called focal hepatic steatosis). This happens when the tip of your catheter is fixed or in very close proximity to your liver.

► **Side effects reported with the implantable pump** (including side effects related to implantation of the pump and or pump maintenance)
Side effects reported commonly
- Change of the pump due to malfunction
- Pump blockage
- Catheter occlusion
- Infection of space where the pump has been implanted (pump pocket)
- Skin erosion: the movements of the pump can erode your skin
- Outward bulge in the navel area (Umbilical hernia)
- Stomach ache
- Pain due to the catheter positioning

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Insuman Implantable

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the vial after 'EXP'. The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C). Do not freeze. Do not put Insuman Implantable next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

In the pump
The medicine is stable in the pump for 45 days at 37°C.

6. Contents of the pack and other information

What Insuman Implantable contains
- The active substance is insulin human. One ml of Insuman Implantable contains 400 IU (International Units) of the active substance insulin human.
- The other ingredients are: phenol, zinc chloride, trometamol, poloxamer 171, glycerol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) (see section 2 under "Important information about some of the ingredients of Insuman Implantable"), water for injections.

What Insuman Implantable looks like and contents of the pack
Insuman Implantable is a clear, colourless or almost colourless solution for infusion, practically free from visible particles, and of a water-like consistency.

Insuman Implantable is supplied in vials containing 10 ml solution (4,000 IU). Packs of 1 and 5 vials of 10 ml are available. Not all pack-sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
sanofi-aventis, s.r.o.
Tel: +420 233 086 111

Danmark
Sanofi A/S
Tlf: +45 45 16 70 00

Lietuva
Swixx Biopharma UAB
Tel: +370 5 236 91 40

Luxembourg/Luxemburg
Sanofi Belgium
Tél/Tel: +32 (0)2 710 54 00
(Belgique/Belgien)

Magyarország
SANOFI-AVENTIS Zrt.
Tel.: +36 1 505 0050

Malta
Sanofi S.r.l.
Tel: +39 02 39394275

Deutschland
Sanofi-Aventis Deutschland GmbH
Tel: 0800 52 52 010
Tel. aus dem Ausland: +49 69 305 21 131

Eesti
Swixx Biopharma OÜ
Tel: +372 640 10 30

Ελλάδα
Sanofi-Aventis Μονοπρόσωπη ΑΕΒΕ
Τηλ: +30 210 900 16 00

España
sanofi-aventis, S.A.
Tel: +34 93 485 94 00

France
Sanofi Winthrop Industrie
Tél: 0 800 222 555
Appel depuis l'étranger: +33 1 57 63 23 23

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +353 (0) 1 403 56 00

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sanofi S.r.l.
Tel: 800 13 12 12 (domande di tipo tecnico)
800 536389 (altre domande)

Κύπρος
C.A. Papaellinas Ltd.
Τηλ: +357 22 741741

Latvija
Swixx Biopharma SIA
Tel: +371 6 616 47 50

Nederland
Sanofi B.V.
Tel: +31 20 245 4000

Norge
sanofi-aventis Norge AS
Tlf: +47 67 10 71 00

Österreich
sanofi-aventis GmbH
Tel: +43 1 80 185 – 0

Polska
sanofi-aventis Sp. z o.o.
Tel.: +48 22 280 00 00

Portugal
Sanofi - Produtos Farmacêuticos, Lda.
Tel: +351 21 35 89 400

România
Sanofi Romania SRL
Tel: +40 (0) 21 317 31 36

Slovenija
Swixx Biopharma d.o.o.
Tel: +386 1 235 51 00

Slovenská republika
Swixx Biopharma s.r.o.
Tel: +421 2 208 33 600

Suomi/Finland
Sanofi Oy
Puh/Tel: +358 (0) 201 200 300

Sverige
Sanofi AB
Tel: +46 (0)8 634 50 00

United Kingdom (Northern Ireland)
sanofi-aventis Ireland Ltd. T/A SANOFI
Tel: +44 (0) 800 035 2525

This leaflet was last revised in {date}

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are diabetic.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?

Examples include:
- you have not administered your insulin or not administered enough, e.g. due to pump not working properly or catheter blockage.
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, are having an operation, have an infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Implantable").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate (pee), tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach ache, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you administer too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Insuman Implantable").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions, loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if

- you are elderly, if you have had diabetes for a long time or if you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you have recently changed from an animal insulin to a human insulin such as Insuman,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Insuman Implantable").

If this happens, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia

1. Do not administer insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Beware: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have talked to you about this before.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if itcomes back.

Tell your relatives, friends and close colleagues the following:

If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.