ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Inpremzia 1 international unit/ml solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bag contains 100 ml equivalent to 100 international units (equivalent to 3.5 mg). 1 ml solution contains 1 international unit insulin human*.

*Produced in *Pichia pastoris* by recombinant DNA technology.

Excipient with known effect

Each bag contains approximately 17 mmol sodium (approximately 386 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless and aqueous solution.
The pH range is 6.5 – 7.2 and the osmolality range is 255–345 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inpremzia is indicated for the treatment of diabetes mellitus.

4.2 Posology and method of administration

Posology

The potency of insulin human is expressed in international units.

Inpremzia dosing is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1 international unit/kg/day. Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations

Elderly (≥ 65 years old)
Inpremzia can be used in elderly patients.
In elderly patients, glucose monitoring should be intensified, and the insulin dose adjusted on an individual basis.

Renal and hepatic impairment
Renal or hepatic impairment may reduce the patient's insulin requirements.
In patients with renal or hepatic impairment, glucose monitoring should be intensified and the Inpremzia dose adjusted on an individual basis.

Paediatric population
Inpremzia can be used in children and adolescents.

Transfer from other insulin medicinal products

When transferring from other insulin medicinal products, adjustment of the insulin human dose may be necessary.

Close glucose monitoring is recommended during the transfer, while the patient is receiving short term therapy with Inpremzia, and upon transfer back to previous insulin therapy (see section 4.4).

Method of administration

Inpremzia is a fast-acting human insulin. It is administered intravenously as an infusion. This should be carried out by healthcare professionals.

The infusion rate should be adjusted according to the individual circumstances and blood glucose levels. Monitoring of blood glucose is necessary during the insulin infusion.

For detailed instructions, please refer to the end of the package leaflet.

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 medicinal product should be clearly recorded.

Visual inspection

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use only if the solution is clear, without visible particles and the container is undamaged. Administer immediately following the insertion of infusion set.

Hyperglycaemia

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. Usually, the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth and loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. In case of hypoglycaemia or if hypoglycaemia is suspected, Inpremzia must not be used. After stabilisation of the patient's blood glucose, adjustment of the dose should be considered (see sections 4.8 and 4.9).

Patients whose blood glucose control is greatly improved, e.g., by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes.

Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin.

Transfer from other insulin medicinal products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal insulin, human insulin, or insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dose.

As treatment with Inpremzia is not intended for the long term, following treatment, patients can continue to use any other type of insulin they have been prescribed.

Injection/infusion site reactions

As with any insulin therapy, infusion site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling, and itching. Reactions usually resolve in a few days to a few weeks. On rare occasions, infusion site reactions may require discontinuation of treatment with this medicinal product.

Combination of Inpremzia 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 Inpremzia 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.

Excipients (sodium)

This medicinal product contains 386 mg sodium (approximately 17 mmol) in each 100 ml infusion bag, equivalent to 20% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Inpremzia is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with glucose metabolism.

The following substances may reduce the patient's insulin requirement:
Oral antidiabetic medicinal products, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids, and sulfonamides.

The following substances may increase the patient's insulin requirement:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no restrictions on treatment of diabetes with insulin during pregnancy, as insulin does not pass the placental barrier.

Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death *in utero*. Intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements normally return rapidly to pre-pregnancy values.

Breast-feeding

There is no restriction on treatment with Inpremzia during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the dose may need to be adjusted.

Fertility

Animal reproduction studies with insulin human have not revealed any adverse effects on fertility.

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. This may constitute a risk in situations where these abilities are of special importance (e.g., driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see Description of selected adverse reactions below.

At the beginning of the insulin treatment, refraction anomalies, oedema and injection/infusion site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection/infusion site) may occur. These reactions are usually of a transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary

worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Tabulated list of adverse reactions

The adverse reactions listed below are based on clinical trial data and classified according to MedDRA frequency and system organ class. Frequency categories are defined according to the following convention: 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).

Immune system disorders	Uncommon – urticaria, rash
	Very rare – anaphylactic reactions*
Metabolism and nutrition disorders	Very common – hypoglycaemia*
Nervous system disorders	Uncommon – peripheral neuropathy (painful neuropathy)
Eye disorders	Uncommon – refraction disorders
	Very rare – diabetic retinopathy
General disorders and administration site conditions	Uncommon – injection/infusion site reactions
	Uncommon – oedema

* see "Description of selected adverse reactions"

Description of selected adverse reactions

Anaphylactic reactions

The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulty in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life threatening.

Hypoglycaemia

The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentrating, drowsiness, excessive hunger, vision changes, headache, nausea, and palpitation.

In clinical trials of insulin human, the frequency of hypoglycaemia varied with patient population, dose regimens and level of glycaemic control.

Paediatric population

Based on post-marketing sources and clinical trials of insulin human, the frequency, type and severity of adverse reactions observed in the paediatric population do not indicate any differences to the broader experience in the general population.

Other special populations

Based on post-marketing sources and clinical trials of insulin human, the frequency, type, and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

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

A specific overdose of insulin cannot be defined, however, hypoglycaemia may develop over sequential stages if too high a dose relative to the patient's requirement is administered.

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.
  Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal products used in diabetes, insulins and analogues for injection, fast-acting, insulin (human), ATC code: A10AB01.

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

Mechanism of action and pharmacodynamic effects

The blood glucose lowering effect of insulin is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

A clinical trial in a single intensive care unit treating hyperglycaemia (blood glucose above 10 mmol/L) in 204 diabetic and 1344 non-diabetic patients undergoing major surgery showed that normoglycaemia (blood glucose 4.4–6.1 mmol/L) induced by intravenous insulin reduced mortality by 42% (8% versus 4.6%).

Inpremzia is a fast-acting insulin which is administered by intravenous infusion.

The time course of insulin action (i.e., glucose lowering) may vary considerably in different individuals, within the same individual, and different doses.

5.2 Pharmacokinetic properties

Insulin in the blood stream has a half-life of a few minutes. Consequently, the time-action profile of an insulin preparation is determined solely by its absorption characteristics.

Inpremzia is administered intravenously and therefore typical patient factors that influence absorption such as injection site and thickness of subcutaneous fat do not impact the pharmacokinetic profile as the product immediately reaches the patient's systemic circulation.

Absorption

In comparison to subcutaneously administered insulin which have a peak insulin effect between 1.5 and 2.5 hours post dose, serum insulin concentrations increase rapidly immediately upon administration by intravenous infusion.

Distribution

No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

Biotransformation

Human insulin is reported to be degraded by insulin protease or insulin-degrading enzymes and possibly protein disulfide isomerase. A number of cleavage (hydrolysis) sites on the insulin human molecule have been proposed; none of the metabolites formed following the cleavage are active.

Elimination

The elimination half-life of Insulin is a few minutes.

Paediatric population

No studies on the pharmacokinetics of Inpremzia have been performed in pediatric patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium dihydrogen phosphate, monohydrate
Disodium hydrogen phosphate, anhydrous
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Before opening

2 years stored in a refrigerator (2 °C – 8 °C).

Inpremzia may be stored at temperatures below 25 °C for a single period of up to 30 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. Inpremzia must not be returned to refrigerated storage.

After insertion of infusion set to the bag

The medicinal product should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 °C–8 °C). Do not freeze.

Keep the bag in the carton in order to protect from light during refrigerated storage.

For storage conditions up to 25 °C, see section 6.3.

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

6.5 Nature and contents of container and special equipment for use, administration or implantation

Infusion bag: 100 ml of solution in a laminate plastic (polyethylene, nylon, polyvinylidene chloride) bag, with a plastic (polyolefin) infusion port.

Pack size of 12 infusion bags of 100 ml. Each single bag is packed in an intermediate cardboard carton.

6.6 Special precautions for disposal and other handling

For single use only.

This medicinal product is a ready-to-use solution for infusion. It does not contain a medication port and must not be mixed with other medicinal products.

The infusion bag should be inspected and if the solution is not clear and colourless, contains particulate matter or if the bag is damaged or in case of leaks, it should not be used. This medicinal product should not be used if it has been frozen.

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

7. MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542 CE Utrecht
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1644/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY 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

Biocon Biologics Limited
20th K.M. Hosur Road
Electronics City
Bangalore, Karnataka 560100
India

Name and address of the manufacturer(s) responsible for batch release

Baxter S.A.
Boulevard René Branquart 80,
7860 Lessines,
Belgium

Baxter Distribution Center Europe S.A.
Chemin de Papignies 17B,
7860 Lessines,
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT

Inpremzia 1 international unit/ml solution for infusion
insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each bag contains 100 ml equivalent to 100 international units (equivalent to 3.5 mg).
1 ml solution contains 1 IU insulin human.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride; sodium dihydrogen phosphate, monohydrate; disodium hydrogen phosphate, anhydrous; water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
12 bags of 100 ml
100 IU/100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single-use only. Ready to use.
Read the package leaflet before use.
Intravenous 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

Do not use if:
- the solution is not clear and colourless, or if solid particles are visible.
- the infusion bag is damaged or in case of leaks.
- the medicine has been frozen.

8. EXPIRY DATE

EXP

After insertion of infusion set to the bag, the medicine should be used immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C–8 °C). Do not freeze.

Can be stored at temperatures below 25°C for a single period of up to 30 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. Inpremzia must not be returned to refrigerated storage.

Keep the bag in the carton in order to protect from light during refrigerated storage.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542 CE Utrecht
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1644/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN 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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Inpremzia 1 international unit/ml solution for infusion
insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each bag contains 100 ml equivalent to 100 international units (equivalent to 3.5 mg).
1 ml solution contains 1 IU insulin human.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride; sodium dihydrogen phosphate, monohydrate; disodium hydrogen phosphate, anhydrous; water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 bag of 100 ml
100 IU/100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single-use only. Ready to use.
Read the package leaflet before use.
Intravenous 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

Do not use if:
- the solution is not clear and colourless, or if solid particles are visible.
- the infusion bag is damaged or in case of leaks.
- the medicine has been frozen.

8. EXPIRY DATE

EXP

After insertion of infusion set to the bag, the medicine should be used immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C–8 °C). Do not freeze.

Can be stored at temperatures below 25°C for a single period of up to 30 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. Inpremzia must not be returned to refrigerated storage.

Keep the bag in the carton in order to protect from light during refrigerated storage.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

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14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BAG LABEL

1. NAME OF THE MEDICINAL PRODUCT

Inpremzia 1 international unit/ml solution for infusion
insulin human

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each bag contains 100 ml equivalent to 100 IU (equivalent to 3.5 mg).
1 ml solution contains 1 IU insulin human.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride; sodium dihydrogen phosphate, monohydrate; disodium hydrogen phosphate, anhydrous; water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion.
1 bag of 100 ml
100 IU/100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single-use only. Ready to use.
Read the package leaflet before use.
Intravenous 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

Do not use if:
- the solution is not clear and colourless, or if solid particles are visible.
- the infusion bag is damaged or in case of leaks.
- the medicine has been frozen.

8. EXPIRY DATE

EXP

After insertion of infusion set to the bag, the medicine should be used immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2 °C–8 °C). Do not freeze.

Can be stored at temperatures below 25°C for a single period of up to 30 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. Inpremzia must not be returned to refrigerated storage.

Keep the bag in the carton in order to protect from light during refrigerated storage.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

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3542 CE Utrecht
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1644/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Inpremzia 1 international unit/ml solution for infusion
insulin human

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects that you may get. See the end of section 4 for how to report side effects.

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. See section 4.

What is in this leaflet

1. What Inpremzia is and what it is used for

Inpremzia is insulin human with a fast-acting effect. It is used to reduce the high blood sugar level in patients with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar.

Inpremzia is given by healthcare professionals by an infusion into a vein. It will start to lower your blood sugar shortly after administration and during treatment your blood sugar levels will be carefully monitored to ensure they are well controlled.

2. What you need to know before you are given Inpremzia

Do not use Inpremzia:
- if you are allergic to insulin human or any of the other ingredients of this medicine (listed in section 6).
- if you suspect hypoglycaemia (low blood sugar), see Summary of serious and very common side effects in section 4.
- if it has not been stored correctly or if it has been frozen, see section 5.
- if the insulin does not appear clear and colourless.

If any of these apply, do not use this medicine. Talk to your doctor, pharmacist or nurse for advice.

Warnings and precautions

Some conditions and activities can affect your need for insulin. Talk to your doctor or nurse before you are given Inpremzia if:
- you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- you exercise more than usual or if you want to change your usual diet, as this may affect your blood sugar level.
- you currently have another illness or infection.

Other medicines and Inpremzia
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Some medicines affect your blood sugar level, and this may mean that your insulin dose has to change. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:
- Other medicines for the treatment of diabetes.
- Monoamine oxidase inhibitors (MAOI) (used to treat depression).
- Beta-blockers (used to treat high blood pressure).
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure).
- Salicylates (used to relieve pain and lower fever).
- Anabolic steroids (such as testosterone).
- Sulfonamides (used to treat infections).

Your blood sugar level may rise (hyperglycaemia) if you take:
- Oral contraceptives (birth control pills).
- Thiazides (used to treat high blood pressure or excessive fluid retention).
- Glucocorticoids (such as 'cortisone' used to treat inflammation).
- Thyroid hormone (used to treat thyroid gland disorders).
- Sympathomimetics (such as epinephrine [adrenaline], salbutamol or terbutaline used to treat asthma).
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounce influence on the body's metabolic processes).
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used to treat acromegaly, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise low blood sugar.

Pioglitazone (tablets used for the treatment of Type 2 diabetes)
Some patients with long standing type 2 diabetes 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).

If you have taken any of the medicines listed here, tell your doctor, pharmacist or nurse.

Inpremzia with alcohol
If you drink alcohol, your need for insulin may change as your blood sugar level may either rise or fall. Careful monitoring is recommended.

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 you are given this medicine.

Inpremzia can be used during pregnancy. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, particularly prevention of hypoglycaemia, is important for the health of your baby.

There are no restrictions on treatment with this medicine during breast-feeding.

Driving and using machines
Ask your doctor whether you can drive a car or operate a machine if you have frequent hypoglycaemia or find it hard to recognise hypoglycaemia.

If your blood sugar is low or high, it might affect your concentration and ability to react and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others.

Inpremzia contains sodium
This medicine contains 386 mg sodium (main component of cooking/table salt) in each 100 ml infusion bag. This is equivalent to 20% of the recommended maximum daily dietary intake of sodium for an adult. Talk to your doctor if you have been advised to follow a low salt (sodium) diet.

3. How Inpremzia is given

This medicine is given by doctors or nurses in a health care setting. It is given by intravenous infusion, through an injection into a vein.

The doctor decides the number of units to be administered, and for how long, based on your medical needs. Details regarding the administration process for health care professionals are at the end of this leaflet.

Use in children and adolescents
This medicine can be used in children and adolescents.

Use in special patient groups
If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly. Discuss the use of this medicine with your doctor.

If you are given too much Inpremzia
The amount of Inpremzia is determined by the doctor. During treatment your blood sugar will be monitored to ensure you receive the correct amount (see summary of Serious and very common side effects in section 4). If glucose levels decrease to the hypoglycaemic range, the Inpremzia dose should be decreased and glucose or sugary products given orally in the cases of mild hypoglycaemia. In cases of severe hypoglycaemia glucagon can be given by a trained person or glucose can be given intravenously by a healthcare professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

If you stop using your insulin
Do not stop using your insulin 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.

Serious and very common side effects

Low blood sugar (hypoglycaemia) is a very common side effect which may affect more than 1 in 10 people.

Low blood sugar may occur if you:
- Receive too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.

- Drink alcohol, see section 2 “Inpremzia with alcohol”

Signs of low blood sugar:
Cold sweat; cool pale skin; headache; rapid heartbeat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

Severe low blood sugar can lead to unconsciousness. If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death. You may recover more quickly from unconsciousness with an injection of the hormone glucagon by someone who knows how to use it. If you are given glucagon you will need glucose or a sugar snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital.

What to do if you experience low blood sugar:
During treatment your blood sugar will be monitored, and your dose level will be adjusted by your doctor or nurse if required.

Serious allergic reaction to Inpremzia or one of its ingredients is a very rare side effect, which may affect up to 1 in 10,000 people, but it can be potentially life threatening.

Seek medical advice immediately:
- If signs of allergy spread to other parts of your body.
- If you suddenly feel unwell, and you start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heartbeat; feel dizzy.

If you notice any of these signs, seek medical advice immediately.

List of other side effects

Uncommon side effects (may affect up to 1 in 100 people**)**
- Signs of allergy: Local allergic reactions (pain, redness, hives, inflammation, bruising, swelling, and itching) at the injection/infusion site may occur, these usually disappear within a few days to a few weeks after receiving your insulin. If they do not disappear, or if they spread throughout your body, talk to your doctor immediately. See also Serious allergic reactions above.
- Vision problems: When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.
- Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain. This is called acute painful neuropathy and is usually transient.
- Swollen joints: When you start using insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears. If not, talk to your doctor.

Very rare side effect (may affect up to 1 in 10,000 people**)**
- Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

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 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 Inpremzia

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 infusion bag label, the carton and carton label after 'EXP'. The expiry date refers to the last day of that month.

Before opening
- Store in a refrigerator (2 °C–8 °C).
- This medicine may also be stored at temperatures below 25°C for a single period of up to 30 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. Inpremzia must not be returned to refrigerated storage.

After insertion of infusion set to the bag
- Use the medicine immediately.

Do not use this medicine if:
- you notice that the solution is not clear, and colourless.
- if the infusion bag is damaged or in case of leaks.
- if it has been frozen. Do not freeze.

Keep the bag in the carton while in refrigerated storage in order to protect from light.

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

6. Contents of the pack and other information

What Inpremzia contains
- The active substance is insulin human. Each ml contains 1 international unit (IU) of insulin human. Each bag contains 100 IU of insulin human (equivalent to 3.5 mg) in 100 ml solution for infusion.
- The other ingredients are sodium chloride; sodium dihydrogen phosphate, monohydrate; disodium hydrogen phosphate, anhydrous; water for injections (see section 2 "Inpremzia contains sodium".)

What Inpremzia looks like and contents of the pack
Inpremzia is presented as a ready-to-use solution for infusion in a 100 ml infusion bag. The solution is clear and colourless.

Each pack contains 12 infusion bags. Each single bag is packed in an intermediate cardboard carton.

Marketing Authorisation Holder
Baxter Holding B.V.
Kobaltweg 49
3542 CE Utrecht
Netherlands

Manufacturer
Baxter S.A.
Boulevard René Branquart 80,
7860 Lessines,
Belgium

Baxter Distribution Center Europe S.A.
Chemin de Papignies 17B,
7860 Lessines,
Belgium

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Posology
This medicine is for administration by intravenous infusion by healthcare professionals.

The dose is individualised in accordance with the needs of the patient. Dose may require adjustment in cases of increased physical activity, dietary changes, and changes in patient health status. Adjustment of insulin dose may also be necessary when transferring from other insulin products or administration methods such as subcutaneous injection.

Hypoglycemia may develop if the dose delivered exceeds the patient's requirement and should be treated based on severity according to usual practices for treatment of hypoglycemia.

Preparation and handling
Ready-to-use solution for infusion. For single use only. This medicine does not contain a medication port and must not be mixed with other medicinal products.

Before opening

Store in the refrigerator (2 °C – 8 °C).

This medicine can also be stored outside of refrigerated storage up to a maximum of 25°C for a single period of up to 30 days, but not beyond the original expiry date. The new expiry date must be written on the carton. Inpremzia must not be returned to refrigerated storage.

Keep the bag in the carton in order to protect from light during refrigerated storage.

Do not use this medicine if it has been frozen.

Inspect the infusion bag and do not use if the solution is not clear and colourless, contains particulate matter or if the bag is damaged or leaks.

After insertion of infusion set to the bag

This medicine should be used immediately

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

For safety reasons the name and batch number of Inpremzia should be recorded when administered to a patient.

Incompatibilities
Due to absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Monitoring
Frequent, careful monitoring of blood glucose is required during therapy with this medicine so that the dose may be adjusted in accordance with the needs of the patient. Intensity of monitoring may need to

be increased in elderly patients, patients with renal or hepatic impairment, when patients are transferred from other insulin treatments, or if there are other changes in patient health, diet, or activity status.