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

Awiqli 700 units/mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution contains 700 units of insulin icodec* (equivalent to 26.8 mg insulin icodec).

Each pre-filled pen contains 700 units of insulin icodec in 1 mL solution.
Each pre-filled pen contains 1 050 units of insulin icodec in 1.5 mL solution.
Each pre-filled pen contains 2 100 units of insulin icodec in 3 mL solution.

*produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (FlexTouch).

Clear and colourless isotonic solution with a pH of approximately 7.4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults.

4.2 Posology and method of administration

Posology

This medicinal product is a basal insulin for once-weekly subcutaneous administration. It is intended to be administered on the same day of the week.

The potency of insulin analogues, including insulin icodec, is expressed in units. One (1) unit of insulin icodec corresponds to 1 unit of insulin glargine (100 units/mL), 1 unit of insulin detemir, 1 unit of insulin degludec, or 1 international unit of human insulin.

Awiqli is available in one strength, 700 units/mL. The needed dose is dialled in units. A dose of 10-700 units per injection, in steps of 10 units, can be administered.

In patients with type 1 diabetes mellitus, this medicinal product must be combined with bolus insulin to cover mealtime insulin requirements.

In patients with type 2 diabetes mellitus, this medicinal product can be administered alone or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin. When insulin icodec is added to sulfonylurea therapy, discontinuation or a reduction in the dose of sulfonylurea should be considered. See sections 4.5 and 5.1.

Awiqli is to be dosed in accordance with the individual patient's needs. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose.

Due to the long half-life of insulin icodec, adjustment of dose is not advised during acute illness nor if patients make short-term changes in their physical activity level or usual diet. In these situations, patients should be instructed to consult their healthcare professional for further guidance on other applicable adjustments, e.g., glucose intake or changes to other glucose lowering medication.

Initiation of Awiqli
Patients with type 2 diabetes mellitus (insulin-naïve)
The recommended weekly starting dose is 70 units and followed by individual once-weekly dose adjustments.

Patients newly diagnosed with type 1 diabetes mellitus
The safety and efficacy of Awiqli in newly diagnosed insulin-naïve type 1 diabetes patients have not been established. No data are available. See section 4.4.

Switch from once- or twice-daily basal insulin medicinal products to Awiqli in type 2 and type 1 diabetes
The first once-weekly dose of Awiqli should be administered on the day following the last dose of once- or twice-daily basal insulin.

When switching patients from once- or twice-daily basal insulin, the recommended once-weekly Awiqli dose is the total daily basal dose multiplied by 7. For the first injection only (week 1 dose), a one-time additional 50% Awiqli dose is recommended if seeking faster achievement of glycaemic control in patients with type 2 diabetes. For type 1 diabetes patients, this dose is always recommended (for the first injection only). If the one-time additional 50% Awiqli dose is administered, the week 1 dose should be the total daily basal insulin dose multiplied by 7 and then multiplied by 1.5, rounded to the nearest 10 units (see Table 1).

The one-time additional dose must not be added for the second injection onwards (see section 4.4). The second once-weekly dose of Awiqli is the total daily basal dose multiplied by 7.

The third and subsequent once-weekly doses should be based on the patient's metabolic needs, blood glucose monitoring results, and glycaemic control goal until the desired fasting plasma glucose is achieved. Adjustment of the dose should be made based on the self-monitored fasting glucose values on the day of titration and the two prior days.

Close glucose monitoring is recommended during the switch and in the following weeks. Doses and timing of concurrent bolus insulin products or other concomitant antidiabetic treatment may need to be adjusted.

Table 1 Awiqli dose when switching from once- or twice-daily basal insulin for type 2 diabetes and type 1 diabetes patients, in case initially (week 1) a one-time additional dose is administered

Previous total daily dose of once- or twice-daily basal insulin (units)	**Recommended Awiqli once-weekly dose (units)[a]**	
	Week 1[b]	Week 2[c]
10	110	70
11	120	80
12	130	80
13	140	90
14	150	100
15	160	110

Previous total daily dose of once- or twice-daily basal insulin (units)	**Recommended Awiqli once-weekly dose (units)[a]**	
	Week 1[b]	Week 2[c]
16	170	110
17	180	120
18	190	130
19	200	130
20	210	140
21	220	150
22	230	150
23	240	160
24	250	170
25	260	180
26	270	180
27	280	190
28	290	200
29	300	200
30	320	210
40	420	280
50	530	350
100	1050[d]	700

[a] all doses are rounded to the nearest 10 units
[b] 1.5 x previous total daily basal insulin dose multiplied by 7. One-time additional dose given in week 1 is recommended if seeking faster achievement of glycaemic control in type 2 diabetes patients. For type 1 diabetes patients, this dose is always recommended
[c] previous total daily basal insulin dose multiplied by 7
[d] when the required dose is larger than the maximum dose stop of the pre-filled pen (700 units), split dose with two injections may be needed.

Missed dose
If a dose is missed, it is recommended that it is administered as soon as possible.

Type 1 diabetes patients

Type 1 diabetes patients must be instructed to continue their dosing once weekly. The once weekly dosing schedule will then be changed to the day of the week where the missed dose was administered. Monitoring of fasting plasma glucose should be performed.

If the original day of once-weekly administration is to be maintained, the time between subsequent doses can be successively extended to finally obtain the same administration day.

Type 2 diabetes patients

If it is still within 3 days of the missed dose, the type 2 diabetes patient can then resume their original once weekly dosing schedule. Monitoring of fasting blood glucose should be performed.

If more than 3 days have passed, the missed dose should still be administered as soon as possible. The once weekly dosing schedule will then be changed to the day of the week where the missed dose was administered. If the original day of once-weekly administration is to be maintained, the time between subsequent doses can be successively extended to finally obtain the same administration day.

Special populations

Elderly
No dose adjustment is required for elderly patients (see section 4.8).

Renal impairment
No dose adjustment is required for patients with renal impairment. In patients with renal impairment, more frequent glucose monitoring is recommended (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with hepatic impairments. In patients with hepatic impairment, more frequent glucose monitoring is recommended (see section 5.2).

Paediatric population
The safety and efficacy of Awiqli in children and adolescents below 18 years have not yet been established. No data are available.

Method of administration

Subcutaneous use only.

Awiqli must not be administered intravenously as it may result in severe hypoglycaemia.
This medicinal product must not be administered intramuscularly as it may change the absorption.
This medicinal product must not be used in insulin infusion pumps.

Awiqli is administered subcutaneously by injection in the thigh, the upper arm or the abdominal wall. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4).

Patients should be instructed to always use a new needle. The reuse of pre-filled pen needles increases the risk of blocked needles, which may cause under- or overdosing. In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet.

Awiqli is available in a pre-filled pen. The dose window shows the number of units of insulin icodec to be injected. No dose recalculation is required. The pre-filled pen delivers 10-700 units in steps of 10 units.

Awiqli must not be drawn from the cartridge of the pre-filled pen into a syringe (see section 4.4).

For further information before administration 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.

Hypoglycaemia

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.5, 4.8 and 4.9).

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

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 concentration, drowsiness, excessive hunger, vision changes, headache, nausea, and palpitation.

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 must be advised accordingly. Usual warning symptoms may disappear in patients with long-standing diabetes. The possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Patient adherence to the dose 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. 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, fever)
- inadequate food intake and 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).

The prolonged effect of Awiqli may delay recovery from hypoglycaemia. Upon onset of a hypoglycaemic episode, patient is recommended to closely measure blood glucose until recovery.

Patients with type 1 diabetes

For type 1 diabetes patients treated with insulin icodec there was a higher risk of hypoglycaemia compared to insulin degludec (see sections 4.8 and 5.1). Patients with type 1 diabetes should only be treated with insulin icodec if a clear benefit from a once weekly posology is expected.

The safety and efficacy of insulin icodec in newly diagnosed insulin-naïve type 1 diabetes patients have not been established. No data are available.

Hyperglycaemia

Administration of rapid-acting insulin is recommended in situations with severe hyperglycaemia. Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Furthermore, concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement.

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, loss of appetite as well as acetone odour of breath. Untreated hyperglycaemia may eventually lead to diabetic ketoacidosis, which is potentially lethal.

Switch between other insulins and insulin icodec

Switching a patient between another insulin medicinal product and insulin icodec should be done under medical supervision and may result in the need for a change in dosage (see section 4.2).

During switch from daily basal insulin to weekly insulin icodec, medication errors can occur in the form of e.g., overdose, dosing errors or forgetting to remove the recommended one-time additional dose after the first injection. These errors might result in hypoglycaemia, hyperglycaemia and/or other clinical consequences. Therefore, patients must be instructed to check that they inject the correct dose, especially for the first and second injections (see sections 4.2 and 4.9).

Patients who are uncertain about the correct dose must be instructed to consult their physician for further guidance.

Lipodystrophy and cutaneous amyloidosis

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 from an affected to an unaffected area, and dose adjustment of antidiabetic medicinal products may be considered.

Eye disorder

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.

Avoidance of medication errors

Patients must be instructed to always check the label on the insulin pen before each injection to avoid accidental mix-ups between once-weekly insulin icodec and other insulin products. Patients must visually verify the dialled units on the dose counter of the pre-filled pen. Patients who are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the pre-filled pen.

To avoid dosing errors and potential overdose, patients and healthcare professionals should never use a syringe to draw the medicinal product from the cartridge in the pre-filled pen.

In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet.

Immunogenicity

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia (see sections 5.1 and 5.2).

Combination of pioglitazone and insulin medicinal products

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., it is essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Medicinal products that may reduce the insulin requirement

Antidiabetic medicinal products, GLP-1 receptor agonists, sulfonylurea, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids, and sulfonamides.

The following substances may increase the insulin requirement

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

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

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

Beta-blockers may mask the symptoms of hypoglycaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no clinical experience with use of insulin icodec in pregnant women.

Animal reproduction studies with insulin icodec have not revealed any effects regarding embryotoxicity and teratogenicity.

Because of lack of experience during pregnancy, women of childbearing potential should be advised to discontinue Awiqli, if they become pregnant or wish to become pregnant.

Breast-feeding

It is unknown whether insulin icodec is excreted in human milk. Available pharmacodynamic/toxicological data in rats have shown excretion of insulin icodec in milk. A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from insulin icodec therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Animal reproduction studies with insulin icodec have not revealed any adverse reactions on fertility.

4.7 Effects on ability to drive and use machines

Awiqli has no or negligible influence on the 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 must 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 clinical trials with insulin icodec is hypoglycaemia (see sections 4.4 and 5.1).

Tabulated list of adverse reactions

The overall safety profile of insulin icodec is based on six phase 3 (ONWARDS 1-6) trials where a total of 2 170 patients were exposed to insulin icodec, 1 880 with type 2 diabetes and 290 with type 1 diabetes.

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA 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) and not known (cannot be estimated from the available data).

Table 2 Tabulated list of adverse reactions

MedDRA system organ classes	**Very common**	**Common**	**Uncommon**	**Rare**
Immune system disorders			Hypersensitivity***	
Metabolism and nutrition disorders	Hypoglycaemia*			
General disorders and administration site conditions		Injection site reaction Peripheral oedema**		
Skin and subcutaneous tissue disorders				Lipodystrophy

* Hypoglycaemia is defined below
** Grouped term covering adverse events related to peripheral oedema
*** Grouped term covering adverse events related to hypersensitivity.

Description of selected adverse reactions

Hypoglycaemia
Hypoglycaemia is the most commonly observed adverse drug reaction in patients using insulin icodec (see sections 4.4 and 5.1).

In phase 3 clinical trials with insulin icodec, severe hypoglycaemia was defined as hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery and clinically significant hypoglycaemia was defined as plasma glucose value less than 54 mg/dL (3.0 mmol/L).

Type 2 diabetes

The proportion of patients reporting severe or clinically significant hypoglycaemic episodes for insulin icodec vs daily basal insulin was 9%-12% vs 6%-11% in insulin naïve type 2 diabetes patients (ONWARDS 1, 3 and 5), 14% vs 7% in type 2 diabetes patients previously treated with basal insulin (ONWARDS 2), and 51% vs 56% in type 2 diabetes patients previously on basal-bolus insulin regimen (ONWARDS 4).

The rates of severe or clinically significant hypoglycaemic episodes per PYE for insulin icodec vs daily basal insulin were as follows: ONWARDS 1: 0.30 vs 0.16; ONWARDS 3: 0.31 vs 0.15; ONWARDS 5: 0.19 vs 0.14 (insulin naïve type 2 diabetes patients); ONWARDS 2: 0.73 vs 0.27 (type 2 diabetes patients previously treated with basal insulin); and ONWARDS 4: 5.64 vs 5.62 (type 2 diabetes patients previously on basal-bolus insulin regimen).

The main phase of ONWARDS 1 trial was followed by an extension part of 26 weeks treatment duration in order to investigate long-term safety. In the complete trial, the proportion of patients with severe or clinically significant hypoglycaemic episodes for insulin icodec vs insulin glargine 100 units/mL was 12% vs 14%, and the rate was 0.30 vs 0.16 episodes per PYE.

For information on daily basal insulin comparators used in each trial, please see section 5.1.

Type 1 diabetes

The proportion of patients reporting severe or clinically significant hypoglycaemic episodes for insulin icodec vs insulin degludec was 85% vs 76% in previously basal insulin-treated patients with type 1 diabetes. The rate of severe or clinically significant hypoglycaemic episodes per PYE for insulin icodec compared to insulin degludec was 19.93 vs 10.37.

ONWARDS 6 trial was followed by an extension part of 26 weeks treatment duration in order to investigate long-term safety. In the complete trial, the proportion of patients with severe or clinically significant hypoglycaemic episodes for insulin icodec vs insulin degludec was 91% vs 86%, and the rate was 17.00 vs 9.16 episodes per PYE.

See also section 5.1.

Across the ONWARDS trials, most hypoglycaemic episodes were observed day 2-4 after the weekly administration.

Hypersensitivity
As with other insulins, allergic reactions may occur with insulin icodec. Immediate-type allergic reactions to either insulin itself or the excipients may potentially be life-threatening.

Hypersensitivity reactions (such as urticaria, lip swelling and swelling face) have been reported in the phase 3a program with insulin icodec. Hypersensitivity reactions were reported in 0.4% of insulin icodec-treated patients compared to 0.6% of daily basal insulin-treated patients. Two out of the 10 events reported by insulin icodec-treated patients were severe (urticaria) and one of these was also reported as serious.

Injection site reactions
In the phase 3 trials, injection site reactions were reported in 1.6% of insulin icodec-treated patients compared to 1.4% of daily basal insulin-treated patients. The majority of injection site reactions in the insulin icodec-treated patients (75%) were reported in the double-blinded, double-dummy, active-controlled trial (ONWARDS 3). In the daily basal insulin-treated patients, 21% of injection site reactions were reported in ONWARDS 3.

Overall, in the phase 3 trials, the most common signs and symptoms of injection site reactions were erythema and pruritus. The maximum severity of injection site reactions for patients treated with insulin icodec was mild (94 %) or moderate (6 %). No injection site reactions were serious.

Skin and subcutaneous tissue disorders
Lipodystrophy (including lipohypertrophy, lipoatrophy) 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).

Other special populations

Based on results from clinical trials with insulin icodec, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not in general indicate any differences to the broader experience in the overall insulin icodec-treated 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 for insulin cannot be defined; however, hypoglycaemia may develop over sequential stages if a patient is dosed with more insulin than required:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or other products containing sugar. It is therefore recommended that the patient always carries sugar-containing products.
- Severe hypoglycaemic episodes, where the patient is not able to treat themselves, can be treated with glucagon given intramuscularly, subcutaneously or intranasally 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.

Overdose events may occur during switch from once- or twice-daily basal insulin to insulin icodec, especially if the one-time additional dose, against recommendation, continues to be administered after the first injection (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, long-acting, ATC code: A10AE07.

Mechanism of action

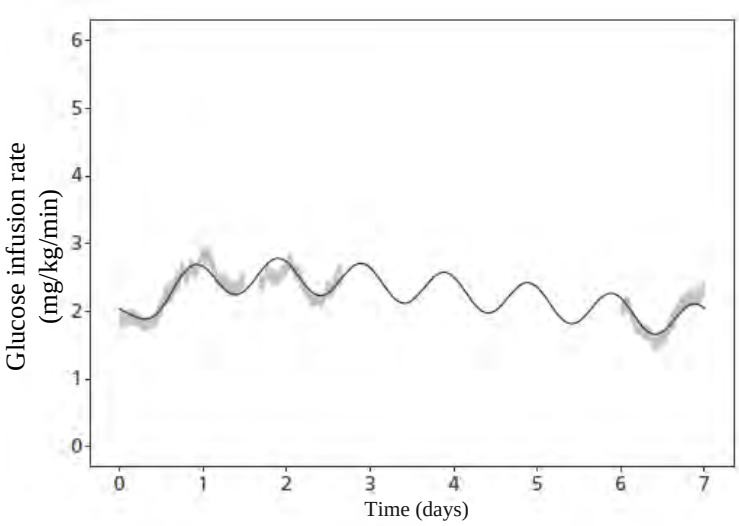
A slow and steady glucose-lowering effect of insulin icodec is driven by albumin binding as well as reduced insulin receptor binding and clearance. The extended half-life of insulin icodec reflects a depot of insulin icodec in the circulation and in the interstitial compartment, from which insulin icodec is slowly and continuously released and binds specifically to the insulin receptor. When insulin

icodec binds to the human insulin receptor it results in the same pharmacological effects as human insulin.

The primary action of insulin, including insulin icodec, is to regulate glucose metabolism. Insulin and its analogues lower blood glucose by activating specific insulin receptors to stimulate peripheral glucose uptake, especially by skeletal muscle and fat as well as to inhibit hepatic glucose production. Insulin also inhibits lipolysis and proteolysis and enhances protein synthesis.

Pharmacodynamic effects

The steady-state pharmacodynamic properties of insulin icodec were investigated in a trial with type 2 diabetes patients. The partial pharmacodynamic properties of insulin icodec were measured in 3 euglycaemic clamps (6.7 mmol/L) during steady state covering 3.5 of the 7 days dosing interval. Glucose infusion rate (GIR) profiles for all three clamps are shown in together with the model-derived data, suggesting the duration of the glucose-lowering effect to cover a full week (Figure 1).



Notes: Shaded areas are standard error of the mean of individual glucose infusion rate (GIR) profiles (pooled across three steady-state weeks). Line is mean of individual model-predicted GIR profiles (for one steady-state week).
Based on data where insulin icodec was injected at 20:00 (corresponding to day 0).

Figure 1 Full-week glucose infusion rate profile of insulin icodec at steady-state in type 2 diabetes

Clinical steady state was reached after 2-4 weeks when initiating insulin icodec without a one-time additional dose and after 2-3 weeks when initiating insulin icodec with a one-time additional dose of 50% with the first dose.

Clinical efficacy and safety

The safety and efficacy of insulin icodec were evaluated in five multinational, randomised, active-controlled, open-label or blinded, parallel-group phase 3 clinical trials of 26 or 52 weeks duration (ONWARDS 1-4 and 6). The trials exposed 1 628 patients to insulin icodec (1 338 in type 2 diabetes mellitus and 290 in type 1 diabetes mellitus). A treat-to-target approach was followed in the trials. The glycaemic target was fasting pre-breakfast self-measured plasma glucose (SMPG) values of 4.4-7.2 mmol/L. Based on the last 3 pre-breakfast SMPG values, the insulin icodec dose was kept stable or adjusted up or down according to trial schedule (weekly or every other week).

The safety and efficacy of insulin icodec were evaluated in insulin-naïve type 2 diabetes mellitus patients (ONWARDS 1 and 3), in type 2 diabetes mellitus patients previously treated with basal insulin (ONWARDS 2), in type 2 diabetes mellitus patients previously treated with basal-bolus regimen (ONWARDS 4) and in patients with type 1 diabetes mellitus (ONWARDS 6). The primary objective for the phase 3 trials was to demonstrate the effect on glycaemic control of once-weekly

insulin icodec compared to a daily basal insulin (insulin degludec or insulin glargine) in the specific diabetes population investigated. This included comparison of the change in HbA_{1c} from baseline to end of treatment with the comparator to confirm non-inferiority. Patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) were excluded from ONWARDS 1-4 and 6.

Patients with type 2 diabetes mellitus
In a 52-week open-label trial with a 26-week extension phase (ONWARDS 1), 984 insulin naïve type 2 diabetes patients were randomised to insulin icodec and insulin glargine (100 units/mL). At baseline, the patients had a mean duration of diabetes of 11.5 years, mean HbA_{1c} of 69 mmol/mol (8.5%), mean fasting plasma glucose (FPG) of 10.3 mmol/L and a mean BMI of 30.1 kg/m^2 (Table 3).

In a 26-week double blind trial (ONWARDS 3), 588 insulin naïve type 2 diabetes patients were randomised to insulin icodec and insulin degludec (100 units/mL). At baseline, the patients had a mean duration of diabetes of 11.3 years, mean HbA_{1c} of 69 mmol/mol (8.5%), mean FPG of 10.1 mmol/L and a mean BMI of 29.6 kg/m^2. The trial was stratified according to region and treatment with sulfonylurea or glinides (Table 3).

In a 26-week open-label trial (ONWARDS 2), 526 basal insulin treated type 2 diabetes patients were randomised to insulin icodec and insulin degludec (100 units/mL). At baseline, the patients had a mean duration of diabetes of 16.7 years, mean HbA_{1c} of 65 mmol/mol (8.1%), mean FPG of 8.4 mmol/L and a mean BMI of 29.3 kg/m^2 (Table 4).

In a 26-week open-label trial (ONWARDS 4), 582 basal-bolus treated type 2 diabetes patients were randomised to insulin icodec and insulin glargine (100 units/mL). At baseline, the patients had a mean duration of diabetes of 17.1 years, mean HbA_{1c} of 67 mmol/mol (8.3%), mean FPG of 9.4 mmol/L and a mean BMI of 30.3 kg/m^2 (Table 5).

The trials with type 2 diabetes mellitus patients allowed the maintenance of current non-insulin anti-diabetic treatment at the same dose level, except for glinides or sulfonylureas. To minimise the risk of hypoglycaemia, treatment with glinides or sulfonylureas was to be discontinued (ONWARDS 1-2 and 4) or reduced by approximately 50% at randomisation (ONWARDS 3).

Table 3 Results from double-blinded (26 weeks) and open-label (52 weeks) clinical trials in adults with type 2 diabetes mellitus (insulin naïve) – ONWARDS 3 and ONWARDS 1

	26 weeks of treatment – ONWARDS 3		52 weeks of treatment – ONWARDS 1	
	Insulin icodec	**Insulin degludec**	**Insulin icodec**	**Insulin glargine 100 units/mL**
N (Full Analysis Set)	294	294	492	492
HbA_{1c} (mmol/mol)				
Baseline	69.96	69.23	69.44	68.79
End of trial*	52.42	54.71	52.21	54.34
Change from baseline*	-17.18	-14.88	-16.91	-14.78
Estimated difference	-2.30 [-3.73; -0.87][a]		-2.13 [-3.93; -0.32][a]	
HbA_{1c} (%)				
Baseline	8.55	8.48	8.50	8.44
End of trial*	6.95	7.16	6.93	7.12
Change from baseline*	-1.57	-1.36	-1.55	-1.35
Estimated difference	-0.21 [-0.34; -0.08][a]		-0.19 [-0.36; -0.03][a]	
Patients (%) achieving HbA_{1c}				

	26 weeks of treatment – ONWARDS 3		52 weeks of treatment – ONWARDS 1	
	Insulin icodec	**Insulin degludec**	**Insulin icodec**	**Insulin glargine 100 units/mL**
< 7% without level 2 or 3 hypoglycaemia[*]	52.13	39.86	52.56	42.58
Estimated odds ratio	1.64 [1.16; 2.33][b, c]		1.49 [1.15; 1.94][b, c]	
Fasting plasma glucose (mmol/L)				
Baseline	10.37	9.78	10.28	10.31
End of trial[*]	7.06	7.08	6.95	6.96
Change from baseline[*]	-3.01	-2.99	-3.35	-3.33
Estimated difference	-0.02 [-0.34; 0.29][b]		-0.01 [-0.27; 0.24][b]	
Time in Range (3.9-10.0 mmol/L) (%)				
Weeks 48-52	N/A		71.94	66.90
Estimated difference	N/A		4.27 [1.92; 6.62]; p< 0.001[a, d]	
Rate of hypoglycaemia per PYE (percentage of patients)				
Level 2	0.31 (8.9)	0.13 (5.8)	0.29 (9.8)	0.15 (10.0)
Estimated rate ratio	2.09 [0.99; 4.41][b]		1.67 [0.99; 2.84][b]	
Level 3	0 (0)	0.01 (0.7)	<0.01 (0.2)	0 (0.6)
Level 2 or level 3	0.31 (8.9)	0.15 (6.1)	0.30 (9.8)	0.16 (10.6)
Estimated rate ratio	1.82 [0.87; 3.80][b]		1.64 [0.98; 2.75][b]	

PYE = patient years of exposure
The 95% confidence interval is stated in "[]"
[*] Least Squares (LS) mean
[a] p< 0.05 for superiority, adjusted for multiplicity
[b] no correction for multiplicity
[c] higher odds of achieving HbA_{1c} target without level 3 or level 2 hypoglycaemia in the prior 12 weeks in patients treated with insulin icodec
[d] 4.27% corresponds to approximately 61 minutes more spent within range per day.

Table 4 Results from open-label clinical trial in adults with type 2 diabetes mellitus (patients previously treated with basal insulin only) – ONWARDS 2

	26 weeks of treatment	
	Insulin icodec	**Insulin degludec**
N (Full Analysis Set)	263	263
HbA_{1c} (mmol/mol)		
Baseline	65.76	65.02
End of trial[*]	55.19	57.64
Change from baseline[*]	-10.20	-7.75
Estimated difference	-2.45 [-4.05; -0.84][a]	
HbA_{1c} (%)		
Baseline	8.17	8.10
End of trial[*]	7.20	7.42
Change from baseline[*]	-0.93	-0.71
Estimated difference	-0.22 [-0.37; -0.08][a]	
Patients (%) achieving HbA_{1c}		

	26 weeks of treatment	
	Insulin icodec	**Insulin degludec**
< 7% without level 2 or 3 hypoglycaemia*	36.73	26.79
Estimated odds ratio	1.59 [1.07; 2.36][b, c]	
Fasting plasma glucose (mmol/L)		
Baseline	8.45	8.36
End of trial*	6.83	6.79
Change from baseline*	-1.58	-1.62
Estimated difference	0.04 [-0.28; 0.36][b]	
Time in Range (3.9-10.0 mmol/L) (%)		
Weeks 22-26	63.13	59.50
Estimated difference	2.41 [-0.84; 5.65] [b, d]	
Rate of hypoglycaemia per PYE (percentage of patients)		
Level 2	0.73 (14.1)	0.27 (7.2)
Estimated rate ratio	1.98 [0.95; 4.12][b]	
Level 3	0 (0)	0.01 (0.4)
Level 2 or level 3	0.73 (14.1)	0.27 (7.2)
Estimated rate ratio	1.93 [0.93; 4.02][b]	

PYE = patient years of exposure
The 95% confidence interval is stated in "[]"
* Least Squares (LS) mean
[a] p< 0.05 for superiority, adjusted for multiplicity
[b] no correction for multiplicity
[c] higher odds of achieving HbA_{1c} target without level 3 or level 2 hypoglycaemia in the prior 12 weeks in patients treated with insulin icodec
[d] 2.41% corresponds to approximately 35 minutes more spent within range per day.

Table 5 Results from open-label clinical trial in adults with type 2 diabetes mellitus (patients previously treated with basal-bolus regimen) – ONWARDS 4

	26 weeks of treatment	
	Insulin icodec	**Insulin glargine 100 units/mL**
N (Full Analysis Set)	291	291
HbA_{1c} (mmol/mol)		
Baseline	67.11	67.35
End of trial*	54.58	54.35
Change from baseline*	-12.65	-12.88
Estimated difference	0.22 [-1.20; 1.65][a]	
HbA_{1c} (%)		
Baseline	8.29	8.31
End of trial*	7.14	7.12
Change from baseline*	-1.16	-1.18
Estimated difference	0.02 [-0.11; 0.15][a]	
Patients (%) achieving HbA_{1c}		

	26 weeks of treatment	
	Insulin icodec	**Insulin glargine 100 units/mL**
< 7% without level 2 or 3 hypoglycaemic episodes*	26.48	25.24
Estimated odds ratio	1.07 [0.73; 1.55][b]	
Fasting plasma glucose (mmol/L)		
Baseline	9.24	9.60
End of trial*	7.67	7.81
Change from baseline*	-1.75	-1.61
Estimated difference	-0.14 [-0.59; 0.31][b]	
Time in Range (3.9-10.0 mmol/L) (%)		
Weeks 22-26	66.88	66.44
Estimated difference	0.29 [-2.52; 3.09][b, c]	
Rate of hypoglycaemia per PYE (percentage of patients)		
Level 2	5.60 (50.9)	5.61 (55.0)
Estimated rate ratio	0.99 [0.73; 1.34][b]	
Level 3	0.04 (1.4)	0.02 (0.7)
Estimated rate ratio	2.19 [0.20; 24.44][b]	
Level 2 or level 3	5.64 (51.5)	5.62 (55.7)
Estimated rate ratio	0.99 [0.73; 1.33][b]	

PYE = patient years of exposure
The 95% confidence interval is stated in "[]"
* Least Squares (LS) mean
[a] p< 0.05 for non-inferiority, adjusted for multiplicity. The non-inferiority margin of 0.3% was chosen for this endpoint
[b] no correction for multiplicity
[c] 0.29% corresponds to approximately 4 minutes more spent within range per day.

Patients with type 1 diabetes mellitus
In a 26-week open-label trial with a 26-week extension phase (ONWARDS 6), 582 basal-bolus treated patients with type 1 diabetes were randomised to insulin icodec and insulin degludec (100 units/mL). At baseline, the patients had a mean duration of diabetes of 19.5 years, mean HbA_{1c} of 60 mmol/mol (7.6%), mean FPG of 9.8 mmol/L and a mean BMI of 26.5 kg/m^2. The trial was stratified by pre-trial basal insulin treatment (either twice daily/insulin glargine 300 units/mL or once daily) and HbA_{1c} (either < 8% or ≥ 8%) at screening (Table 6).

Table 6 Results from open-label clinical trial in adults with type 1 diabetes mellitus – ONWARDS 6

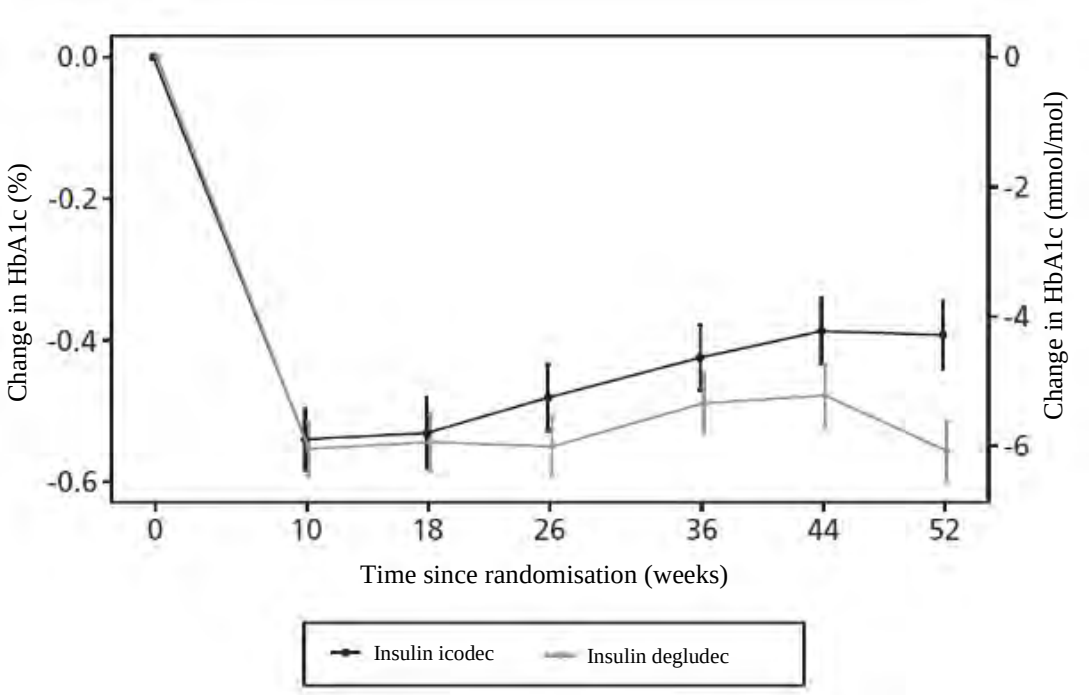
	26 weeks of treatment	
	Insulin icodec	**Insulin degludec**
N (Full Analysis Set)	290	292
HbA_{1c} (mmol/mol)		
Baseline	59.46	59.95
End of trial*	54.62	54.09
Change from baseline*	-5.08	-5.61
Estimated difference	0.53 [-1.46; 2.51][a]	
HbA_{1c} (%)		

	26 weeks of treatment	
	Insulin icodec	**Insulin degludec**
Baseline	7.59	7.63
End of trial*	7.15	7.10
Change from baseline*	-0.47	-0.51
Estimated difference	0.05 [-0.13; 0.23][a]	
Patients (%) achieving HbA_{1c}		
< 7% without level 2 or 3 hypoglycaemic episodes*	9.55	16.74
Estimated odds ratio	0.52 [0.33; 0.85][b, c]	
Fasting plasma glucose (mmol/L)		
Baseline	9.94	9.56
End of trial*	8.91	7.88
Change from baseline*	-0.84	-1.87
Estimated difference	1.03 [0.48; 1.59][b]	
Time in Range (3.9-10.0 mmol/L) (%)**		
Weeks 22-26	59.10	60.85
Estimated difference	-2.00 [-4.38; 0.38][b, d]	
Rate of hypoglycaemia per PYE (percentage of patients)		
Level 2	19.60 (84.8)	10.26 (76.4)
Estimated rate ratio	1.88 [1.53; 2.32][b]	
Level 3	0.33 (3.1)	0.12 (3.1)
Estimated rate ratio	2.08 [0.39; 10.96][b]	
Level 2 or level 3	19.93 (85.2)	10.37 (76.4)
Estimated rate ratio	1.89 [1.54; 2.33][b]	

PYE = patient years of exposure
The 95% confidence interval is stated in "[]"
* Least Squares (LS) mean
** unblinded CGM data was captured from a trial in patients with type 1 diabetes mellitus
[a] p< 0.05 for non-inferiority, adjusted for multiplicity. The non-inferiority margin of 0.3% was chosen for this endpoint
[b] no correction for multiplicity
[c] higher odds of achieving HbA_{1c} target without level 3 or level 2 hypoglycaemia in the prior 12 weeks in patients treated with insulin degludec
[d] -2.00% corresponds to approximately 29 minutes less spent within range per day.

Extension data for ONWARDS 6

In the complete ONWARDS 6 trial, including the 26-week extension phase, in T1DM patients, the reduction in HbA_{1c} from baseline for insulin icodec vs insulin degludec was -0.37% vs -0.54% (Least Squares [LS] mean; estimated treatment difference 0.17 [0.02;0.31]).



Notes: Observed data including data obtained after premature treatment discontinuation. Full analysis set.
Legend: Mean (symbol) ± standard error to mean (error bars).

Figure 2 HbA_{1c} by treatment week in ONWARDS 6 – change from baseline up to week 52

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of trials with Awiqli in all subsets of the paediatric population (0 to 18 years) for both type 1 and type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

Immunogenicity

In patients with type 2 diabetes, treatment with insulin icodec induced development of anti-drug antibodies (ADA) in 77%-82% of previously insulin-naïve patients (ONWARDS 3 and trial 4383), in 54% of patients previously treated with daily basal insulin (ONWARDS 2) and in 41% of patients previously treated with daily basal-bolus insulin (ONWARDS 4). In the type 1 diabetes population (ONWARDS 6), treatment with insulin icodec induced development of ADA in 33%. ADA titres were increased in 37% of patients with type 1 diabetes that were ADA positive at baseline. Most of the icodec antibody positive patients, in both the type 1 and type 2 diabetes populations, had also cross-reacting antibodies towards human insulin. Overall, the titres of anti-insulin icodec antibodies did not affect the measured clinical efficacy or safety parameters. See also sections 4.4 and 5.2.

Special populations

Improvement in HbA_{1c} was not affected by sex, ethnicity, age, diabetes duration (< 10 years and ≥ 10 years), HbA_{1c} value at baseline (< 8% or ≥ 8%) or baseline body mass index (BMI).

5.2 Pharmacokinetic properties

Overall, pharmacokinetic (PK) properties were similar between groups assessed by population-PK analysis in confirmatory trials, with a trend towards higher exposure with higher anti-drug antibodies (ADA) titres. The effect is not considered clinically relevant as the relative exposure (C_{avg}) was inside the 0.8-1.25 interval when compared to ADA-negative subjects. Overall ADA prevalence was 70-82%. See section 5.1.

Absorption

Insulin icodec is a basal insulin that binds reversibly to albumin, resulting in a slow release of insulin icodec from the essentially inactive depot in circulation and interstitial compartment.

After subcutaneous injection, clinical steady state was reached after 2-4 weeks when initiating insulin icodec without a one-time additional dose and after 2-3 weeks when initiating insulin icodec with a one-time additional dose of 50% with the first dose.

After subcutaneous injection of insulin icodec, the week-to-week intra-subject variability in total exposure is considered low (coefficient of variation for insulin icodec at steady state was 5.90% in type 2 diabetes patients).

Distribution

The affinity of insulin icodec to serum albumin corresponds to a plasma protein binding of > 99% in human plasma. No clinically relevant differences in pharmacokinetics properties of insulin icodec are seen across serum albumin levels.

The results of the *in vitro* protein binding studies demonstrate that there is no clinically relevant interaction between insulin icodec and fatty acids or other protein-bound medicinal products.

Biotransformation

Degradation of insulin icodec is similar to that of human insulin; all metabolites formed are inactive.

Elimination

The half-life after subcutaneous administration is approximately one week independent of dose.

Linearity

Dose proportionality in total exposure is observed after subcutaneous administration within the therapeutic dose range.

Sex, elderly, renal and hepatic impairment

Overall, the pharmacokinetic properties of insulin icodec were preserved and there was no clinically relevant difference in exposure between female and male subjects, between elderly and younger adult subjects (range of studied age of 18-86 years old), or between healthy subjects and subjects with renal or hepatic impairment.

5.3 Pre-clinical safety data

The ratio of mitogenic relative to metabolic potency for insulin icodec is comparable to that of human insulin.

Non-clinical data reveal no special safety concerns for humans based on studies of safety pharmacology, repeated dose toxicity, and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Metacresol
Phenol
Zinc acetate
Sodium chloride
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.

Awiqli must not be added to infusion fluids.

6.3 Shelf life

30 months.

Shelf life after first opening of the pen
After first opening or carried as a spare, the medicinal product may be stored for a maximum of 12 weeks. Store below 30 °C. Can be stored in a refrigerator (2 °C - 8 °C). Keep the cap on the pen in order to protect from light.

6.4 Special precautions for storage

Before first use
Store in a refrigerator (2 °C - 8 °C).
Do not freeze. Keep away from the freezing element.
Keep the cap on the pen in order to protect from light.

After first opening or if carried as a spare
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1, 1.5 or 3 mL solution in a cartridge (type I glass) with a plunger (halobutyl) and a laminated rubber sheet (halobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene. The cap holder for the longer cartridge containing 3 mL (2 100 units solution has a design feature as a clip on the pen injector cap.

The pre-filled pen is designed to be used with disposable needles up to a length of 8 mm.

The pen body is in green while the pen label is in darker green with a yellow box highlighting the strength. The outer packaging is in green with the formulation strength indicated in a yellow-coloured box.

Pack sizes

Awiqli pre-filled pen containing 700 units of insulin icodec in 1 mL solution.
- 1 pre-filled pen (without needles).
- 1 pre-filled pen with 9 disposable NovoFine Plus needles.
- 1 pre-filled pen with 14 disposable NovoFine Plus needles.

Awiqli pre-filled pen containing 1 050 units of insulin icodec in 1.5 mL solution.
- 1 pre-filled pen (without needles).
- 1 pre-filled pen with 13 disposable NovoFine Plus needles.
- 1 pre-filled pen with 14 disposable NovoFine Plus needles.
- Multipack containing 2 (2 packs of 1) pre-filled pens with 26 (2 packs of 13) disposable NovoFine Plus needles.
- Multipack containing 2 (2 packs of 1) pre-filled pens with 28 (2 packs of 14) disposable NovoFine Plus needles.

Awiqli pre-filled pen containing 2 100 units of insulin icodec in 3 mL solution.
- 1 pre-filled pen (without needles).
- 2 pre-filled pens (without needles).
- 1 pre-filled pen with 13 disposable NovoFine Plus needles.
- 1 pre-filled pen with 14 disposable NovoFine Plus needles.
- Multipack containing 2 (2 packs of 1) pre-filled pens with 26 (2 packs of 13) disposable NovoFine Plus needles.
- Multipack containing 2 (2 packs of 1) pre-filled pens with 28 (2 packs of 14) disposable NovoFine Plus needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is for use by one person only.
Awiqli must not be used if the solution does not appear clear and colourless.
Awiqli which has been frozen must not be used.

A new needle must always be attached before each injection. Needles must not be reused. Needles must be discarded immediately after use.

In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet.

For detailed instructions for use, see the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Alle 1
DK-2880 Bagsvaerd
Denmark

8. MARKETING AUTHORISATION NUMBERS

Awiqli 700 units/mL solution for injection in pre-filled pen
EU/1/24/1815/001
EU/1/24/1815/002
EU/1/24/1815/003
EU/1/24/1815/004
EU/1/24/1815/005
EU/1/24/1815/006
EU/1/24/1815/007
EU/1/24/1815/008
EU/1/24/1815/009
EU/1/24/1815/010
EU/1/24/1815/011
EU/1/24/1815/012
EU/1/24/1815/013
EU/1/24/1815/014

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 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 OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novo Nordisk A/S
Hallas Alle 1
DK-4400 Kalundborg
Denmark

Name and address of the manufacturer responsible for batch release

Novo Nordisk A/S
Novo Alle 1
DK-2880 Bagsvaerd
Denmark

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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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.

- **Additional risk minimisation measures**

The MAH shall provide an education guide prior to launch targeting to all patients who will be treated with Awiqli. The educational guide is aimed at increasing awareness about the introduction of the one-time additional dose and describing the key points of use to minimise the risk of medication errors due to mix-up and during switch from daily basal insulin to once-weekly Awiqli in diabetes mellitus.

The educational guide contains information and instructions related to the following key elements:
Medication errors due to switch from daily basal insulin:

- Information on use of one-time additional dose when initiating Awiqli.
- Key differences between first dose and second dose of Awiqli.

Medication errors due to mix-up:

- Instructions to strictly adhere to weekly dosing regimen as prescribed by the healthcare provider.
- Instructions to always check the insulin label before each injection to avoid accidental mix-ups between Awiqli and other products.
- Instructions to always use the dose recommended by the healthcare provider.
- Instructions to always use the dose counter and the dose pointer to select the dose. Do not count the pen clicks to select the dose.
- Instructions to check how many units were selected before injecting the weekly insulin.
- Instructions to patients who are blind or have poor vision to always get help/assistance from another person who has good vision and is trained in using the insulin device.

The MAH shall agree on the final content of the education guide together with a communication plan, with the National Competent Authority in each Member State prior to distribution of the educational guide in the Member State.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (SINGLE PACKS)

1. NAME OF THE MEDICINAL PRODUCT

Awiqli 700 units/mL solution for injection in pre-filled pen
insulin icodec

2. STATEMENT OF ACTIVE SUBSTANCE

1 mL solution contains 700 units of insulin icodec (equivalent to 26.8 mg).

Each pre-filled pen contains 700 units of insulin icodec in 1 mL solution
Each pre-filled pen contains 1 050 units of insulin icodec in 1.5 mL solution
Each pre-filled pen contains 2 100 units of insulin icodec in 3 mL solution

3. LIST OF EXCIPIENTS

Excipients: Glycerol, metacresol, phenol, zinc acetate, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection in pre-filled pen
FlexTouch

1x1 mL pre-filled pen (700 units)
1x1 mL pre-filled pen (700 units) with 9 disposable needles
1x1 mL pre-filled pen (700 units) with 14 disposable needles

1x1.5 mL pre-filled pen (1 050 units)
1x1.5 mL pre-filled pen (1 050 units) with 13 disposable needles
1x1.5 mL pre-filled pen (1 050 units) with 14 disposable needles

1x3 mL pre-filled pen (2 100 units)
2x3 mL pre-filled pen (2 100 units)
1x3 mL pre-filled pen (2 100 units) with 13 disposable needles
1x3 mL pre-filled pen (2 100 units) with 14 disposable needles

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
subcutaneous use

once weekly
The pen shows the dose
One step equals 10 units

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 WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only
Use a new needle for every injection
Needles are not included

8. EXPIRY DATE

EXP
After first opening: Use within 12 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
After first opening: Store below 30 °C. Can be stored in a refrigerator.
Keep the cap on the pen in order to protect it from light

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

Discard the needle safely after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Alle 1
DK-2880 Bagsvaerd
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1815/001 1 pre-filled pen of 1 mL
EU/1/24/1815/002 1 pre-filled pen of 1 mL (with 9 needles)
EU/1/24/1815/003 1 pre-filled pen of 1 mL (with 14 needles)
EU/1/24/1815/004 1 pre-filled pen of 1.5 mL
EU/1/24/1815/005 1 pre-filled pen of 1.5 mL (with 13 needles)
EU/1/24/1815/006 1 pre-filled pen of 1.5 mL (with 14 needles)
EU/1/24/1815/009 1 pre-filled pen of 3 mL
EU/1/24/1815/011 1 pre-filled pen of 3 mL (with 13 needles)
EU/1/24/1815/012 1 pre-filled pen of 3 mL (with 14 needles)
EU/1/24/1815/010 2 pre-filled pens of 3 mL

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Awiqli 700

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

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Awiqli 700 units/mL solution for injection in pre-filled pen
insulin icodec

2. STATEMENT OF ACTIVE SUBSTANCE

1 mL solution contains 700 units of insulin icodec (equivalent to 26.8 mg).

Each pre-filled pen contains 1 050 units of insulin icodec in 1.5 mL solution
Each pre-filled pen contains 2 100 units of insulin icodec in 3 mL solution

3. LIST OF EXCIPIENTS

Excipients: Glycerol, metacresol, phenol, zinc acetate, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection in pre-filled pen
FlexTouch

Multipack: 2 (2 packs of 1) 1.5 mL pre-filled pens (1 050 units) with 26 disposable needles
Multipack: 2 (2 packs of 1) 1.5 mL pre-filled pens (1 050 units) with 28 disposable needles
Multipack: 2 (2 packs of 1) 3 mL pre-filled pens (2 100 units) with 26 disposable needles
Multipack: 2 (2 packs of 1) 3 mL pre-filled pens (2 100 units) with 28 disposable needles

2x1.5 mL
2x3 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
subcutaneous use

once weekly
The pen shows the dose
One step equals 10 units

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 WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only
Use a new needle for every injection

8. EXPIRY DATE

EXP
After first opening: Use within 12 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
After first opening: Store below 30 °C. Can be stored in a refrigerator.
Keep the cap on the pen in order to protect it from light

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

Discard the needle safely after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Alle 1
DK-2880 Bagsvaerd
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1815/007 2 (2 packs of 1) pre-filled pens of 1.5 mL (with 26 needles)
EU/1/24/1815/008 2 (2 packs of 1) pre-filled pens of 1.5 mL (with 28 needles)
EU/1/24/1815/013 2 (2 packs of 1) pre-filled pens of 3 mL (with 26 needles)
EU/1/24/1815/014 2 (2 packs of 1) pre-filled pens of 3 mL (with 28 needles)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Awiqli 700

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 INNER PACKAGING

INNER CARTON FOR MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Awiqli 700 units/mL solution for injection in pre-filled pen
insulin icodec

2. STATEMENT OF ACTIVE SUBSTANCE

1 mL solution contains 700 units of insulin icodec (equivalent to 26.8 mg)

Each pre-filled pen contains 1 050 units of insulin icodec in 1.5 mL solution
Each pre-filled pen contains 2 100 units of insulin icodec in 3 mL solution

3. LIST OF EXCIPIENTS

Excipients: Glycerol, metacresol, phenol, zinc acetate, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
FlexTouch

1x1.5 mL pre-filled pen (1 050 units) with 13 disposable needles. Component of a multipack, cannot be sold separately
1x1.5 mL pre-filled pen (1 050 units) with 14 disposable needles. Component of a multipack, cannot be sold separately
1x3 mL pre-filled pen (2 100 units) with 13 disposable needles. Component of a multipack, cannot be sold separately
1x3 mL pre-filled pen (2 100 units) with 14 disposable needles. Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
subcutaneous use

once weekly
The pen shows the dose
One step equals 10 units

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 WARNINGS, IF NECESSARY

Use only clear, colourless solution
Single patient use only
Use a new needle for every injection

8. EXPIRY DATE

EXP
After first opening: Use within 12 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
After first opening: Store below 30 °C. Can be stored in a refrigerator.
Keep the cap on the pen in order to protect it from light

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

Discard the needle safely after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Alle 1
DK-2880 Bagsvaerd
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1815/007 2 (2 packs of 1) pre-filled pens of 1.5 mL (with 26 needles)
EU/1/24/1815/008 2 (2 packs of 1) pre-filled pens of 1.5 mL (with 28 needles)
EU/1/24/1815/013 2 (2 packs of 1) pre-filled pens of 3 mL (with 26 needles)
EU/1/24/1815/014 2 (2 packs of 1) pre-filled pens of 3 mL (with 28 needles)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Awiqli 700

17. UNIQUE IDENTIFIER - 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Awiqli 700 units/mL solution for injection
insulin icodec
FlexTouch
SC

2. METHOD OF ADMINISTRATION

subcutaneous use
once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL
1.5 mL
3 mL

6. OTHER

Novo Nordisk A/S

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Awiqli 700 units/mL solution for injection in pre-filled pen
insulin icodec

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects 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, 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 Awiqli is and what it is used for

Awiqli contains ‘insulin icodec’ used to treat diabetes in adults. It is a type of insulin called a ‘long-acting basal insulin’.

Diabetes is a disease where your body does not produce enough insulin (a hormone that controls the amount of blood sugar in the body). The active substance in Awiqli, insulin icodec, is a replacement insulin that acts in the same way as naturally produced insulin but works for a longer time. This means that it produces a long and steady blood sugar lowering action. It therefore only needs to be injected once a week.

2. What you need to know before you use Awiqli

Do not use Awiqli
- if you are allergic to insulin icodec 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 Awiqli.

Before you use Awiqli it is important that you are aware of the following:
- Hypoglycaemia (low blood glucose levels) can occur if your dose of Awiqli is too high or if you miss a meal or undertake unplanned, strenuous physical exercise. Other factors that can increase the risk of hypoglycaemia include change of the injection area, illness (such as vomiting, diarrhoea and fever), alcohol consumption and use of other medicines. Symptoms of hypoglycaemia usually occur suddenly (see information in the box at the end of this leaflet). Severe hypoglycaemia may lead to loss of consciousness and/or seizures and may result in

temporary or permanent impairment of brain function or even death. If you experience hypoglycaemia, follow the guidance in the box at the end of this leaflet for low blood sugar.
- If you have type 1 diabetes, the occurrence of hypoglycaemia could be higher
- Hyperglycaemia (high blood glucose levels) can occur if the dose of Awiqli is insufficient and/or if treatment is discontinued or if you have an associated illness, particularly an infection. Symptoms of hyperglycaemia usually develop gradually over a period of hours or days (see information in the box at the end of this leaflet). Untreated hyperglycaemia may lead to diabetic ketoacidosis (a serious complication of diabetes with high levels of ketones in the blood). If you experience hyperglycaemia, follow the guidance in the box at the end of this leaflet for high blood sugar level.
- Switching from other insulin medicines – your doctor may need to adjust the insulin dose if you switch from once or twice a day basal insulin to once a week Awiqli. It is important that you always check that you inject the correct dose, particularly for the first and second injections of Awiqli since your doctor may prescribe you an increased dose for the first injection followed by a lower dose. Always follow your doctor's recommendation on how much medicine you should take. Please see section 3.
- If you are taking pioglitazone with Awiqli, contact your doctor if you have any signs or symptoms of congestive heart failure (when the heart does not pump blood as well as it should) such as shortness of breath, tiredness, fluid retention, weight gain and ankle swelling.
- Eye problems – fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye retinopathy (an eye condition that can cause loss of vision and blindless in people who have diabetes). If you have eye problems, talk to your doctor.
- Make sure you use the right type and dose of insulin – always check the label on your insulin pen before each injection to avoid mix-ups with other insulin products. If you are blind or have poor vision, ensure that you get assistance from another person who has good vision and is trained in using the pre-filled pen.

Skin changes where the injection is given
The injection site should be changed regularly to help prevent changes to the fatty tissue under the skin. Such changes include skin thickening or shrinking or lumps under the skin.

This medicine may not work properly if you inject into a lumpy, shrunken or thickened area (see section 3. How to use Awiqli). Tell your doctor, pharmacists or nurse if you notice any skin changes where the injection is given and if you are currently injecting into these affected areas before you start injecting in a different area. Your doctor, pharmacist or nurse may tell you to check your blood sugar more closely, and to adjust your dose of Awiqli or other antidiabetic medicines dose if needed.

Antibodies to insulin
Treatment with Awiqli can cause the body to produce antibodies to insulin (molecules that can affect treatment with insulin). This may very rarely, require you to change your insulin dose.

Children and adolescents
Do not give this medicine to children and adolescents between the ages of 0 and 18 years. This is because there is no experience with using Awiqli in children or adolescents.

Other medicines and Awiqli
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, this may mean your dose of Awiqli has to be changed.

Listed below are the most common medicines which may affect your treatment with Awiqli.

You may need a lower dose / your blood sugar level may fall (hypoglycaemia) if you take:
- other medicines for diabetes (by mouth or injection)
- sulfonamides, for infections
- anabolic steroids, such as testosterone

- beta-blockers, for example for high blood pressure. They may make it harder to recognise the warning signs of too low blood sugar (see information in the box at the end of this leaflet. Warning signs of too low blood sugar)
- acetylsalicylic acid (and other salicylates), for pain and mild fever
- monoamine oxidase (MAO) inhibitors, for depression
- angiotensin converting enzyme (ACE) inhibitors, for some heart problems or high blood pressure.

You may need a higher dose / your blood sugar level may rise (hyperglycaemia) if you take:
- danazol, for endometriosis
- oral contraceptives (birth control pills)
- thyroid hormones, for thyroid problems
- growth hormone, for growth hormone deficiency
- glucocorticoids such as cortisone, for inflammation
- sympathomimetics such as epinephrine (adrenaline), salbutamol or terbutaline, for asthma
- thiazides, for high blood pressure or if your body keeps too much water (water retention).

Octreotide and lanreotide (for a rare illness involving too much growth hormone (acromegaly)) may increase or decrease your blood sugar level.

Pioglitazone (a diabetes medicine given by mouth for type 2 diabetes).
Some patients with long-standing type 2 diabetes and heart disease or previous stroke treated with pioglitazone and insulin developed heart failure.
- Tell your doctor straight away if you have signs of heart failure – such as shortness of breath, tiredness, fluid retention, weight gain and ankle swelling.

If any of the above applies to you (or you are not sure), talk to your doctor, pharmacist or nurse before injecting Awiqli as the adjustment of the dose of a weekly insulin in relation to interaction with other medicines may be different.

Awiqli with alcohol
If you drink alcohol, the dose of Awiqli you need may change. Your blood sugar level may either rise or fall. This means you need to check your blood sugar level more often than usual when you drink alcohol.

Pregnancy and breast-feeding
It is not known if or how Awiqli may affect a foetus. Therefore, you should stop the treatment with this medicine if you are a woman of childbearing potential trying to conceive. If you get pregnant while using this medicine, contact your doctor for guidance.

It is not known if this medicine is excreted in human milk and a risk for the baby cannot be excluded. Therefore, Awiqli should not be used while breast-feeding and it must be decided if you should stop the treatment with this medicine or if you should avoid breast-feeding.

Driving and using machines
Awiqli has no or negligible effects on the ability to drive and use machines, but it changes your blood sugar levels. Having too low or too high blood sugar can affect your ability to drive or use any tools or machines. If your blood sugar is too low or too high, your ability to concentrate or react might be affected. This could be dangerous to yourself or others. Ask your doctor or nurse for guidance if:
- you often get too low blood sugar
- you find it hard to recognise too low blood sugar.

Important information about some of the ingredients of Awiqli
This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e., it is essentially ‘sodium-free’.

3. How to use Awiqli

Awiqli is given **once a week**.

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Awiqli is a long-acting insulin. It can be used with short or rapid-acting insulins.

In type 2 diabetes:
- Awiqli may be used along with tablets or injections for diabetes - including short or rapid-acting insulins.

In type 1 diabetes:
- Awiqli must always be used along with short or rapid-acting insulins.
- If you are newly diagnosed with type 1 diabetes (you are not on insulin treatment already), Awiqli is not suitable for you.

If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the pre-filled pen.

What the pens contain
The pre-filled pen can provide a dose of 10-700 units in one injection in steps of 10 units.
- Awiqli 700 units/mL (1 mL) contains 700 units
- Awiqli 700 units/mL (1.5 mL) contains 1 050 units
- Awiqli 700 units/mL (3 mL) contains 2 100 units

The dose counter of the pre-filled pen shows the number of units of insulin you should inject. For this reason, do not make any dose recalculation. The pre-filled pen 700 units/mL can provide a dose of 10-700 units in one injection in steps of 10 units.

When to use Awiqli
Awiqli is a basal insulin for use **once a week**.
- You should inject Awiqli on the same day every week.
- You can take the medicine at any time of the day.

How much to inject
Your doctor will decide together with you:
- how much Awiqli you will need each week
- when to check your blood sugar level
- when you need a higher or lower dose - as your doctor may change your dose based on your blood sugar level
- if your treatment needs to be adjusted when using other medicines.

Dose when switching from a once- or twice-daily basal insulin
Your once a week dose of Awiqli depends on your current basal insulin dose. Your doctor will prescribe you the dose that covers your weekly basal insulin need.
- For the first injection only, you may need to take an increased Awiqli dose. This dose is for the first injection only; do not use this dose for the second and following injections. Please talk to your doctor about how much you should take for your first injection.
- Your dose should be based on your blood glucose measurements. Your doctor will decide together with you how much Awiqli you will have each week.
- Close glucose monitoring is recommended during the switch and in the following weeks.

Use in the elderly (65 years and older)
Awiqli can be used in the elderly.

If you have kidney or liver problems
If you have kidney or liver problems, you may need to check your blood sugar level more often.

Before injecting Awiqli
Before you use Awiqli for the first time, read the instructions for use that come with this package. Check the name on the label of the pen to make sure it is Awiqli 700 units/mL.

How to inject
- Inject Awiqli under the skin (subcutaneous injection). Do not inject it into a vein or muscle.
- The best places to inject are your thighs, upper arms or your belly (abdomen).
- Change the place where you inject this medicine each time. This is to reduce the risk of developing lumps and skin pitting (see section 2).
- Always use a new needle for each injection. This reduces the risk of contamination, infection, and blocked needles that may lead to inaccurate dosing. Dispose of needles safely after each use.
- Do not use a syringe to remove the solution from the pen - to avoid dosing errors and potential overdose.

Detailed instructions for use are provided on the other side of this leaflet.

You should not use Awiqli
- in insulin infusion pumps
- if the pen is damaged or has not been stored correctly (see section 5)
- if there are visible particles - the solution should be clear and colourless.

If you use more Awiqli than you should
If you use too much of this medicine, your blood sugar may get too low (hypoglycaemia). See guidance in the information in the box at the end of this leaflet – Too low blood sugar (hypoglycaemia).

If you forget to use Awiqli
<u>If you are a type 1 diabetes patient</u>
- Inject it as soon as you remember. You should then inject Awiqli one week after you have injected the missed dose. This day will become your new weekly injection day for Awiqli. Continue injecting once a week afterwards.
- If you wish to return to your usual injection day, you may do so in agreement with your doctor by extending the time between your next doses.
- If you are unsure when to take your medicine, talk to your doctor or pharmacist.

<u>If you are a type 2 diabetes patient</u>
- If it is 3 days or less after you should have injected Awiqli, inject it as soon as you remember. Then inject your next dose on your usual injection day.
- If it is more than 3 days since you should have injected Awiqli, inject it as soon as you remember. You should inject your next dose of Awiqli one week after you have injected the missed dose. If you wish to return to your usual injection day, you may do so in agreement with your doctor by extending the time between your next doses.
- Continue injecting once a week afterwards.
- If you are unsure when to take your medicine, talk to your doctor or pharmacist.

If you stop using Awiqli
Do not stop using Awiqli without talking to your doctor. If you stop using this medicine, this could lead to a very high blood sugar level (hyperglycaemia) and ketoacidosis (a condition with too much acid in the blood). See advice in the information in the box at the end of this leaflet - Too high blood sugar (hyperglycaemia).

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Hypoglycaemia (too low blood sugar) – very common (may affect more than 1 in 10 people)
- It can be very serious
- If your blood sugar level falls too much, you may pass out.
- Serious hypoglycaemia may cause brain damage and may be life-threatening.

If you have signs of low blood sugar, try to increase your blood sugar level straight away. See advice in 'Too low blood sugar (hypoglycaemia)' below.

Hypersensitivity reactions – uncommon (may affect up to 1 in 100 people)
The signs of a serious allergic reaction are:
- feeling unwell (light-headed)
- difficulty breathing
- fast heartbeat or feeling dizzy
- nausea and vomiting
- local reactions such as rash, swelling, or itching that spread to other parts of your body
- sweating and loss of consciousness.

If you have a serious allergic reaction to Awiqli, stop using this medicine and see a doctor straight away. Serious allergic reaction can be life threatening if throat swelling blocks the airway.

Skin changes where the injection is given – rare (may affect up to 1 in 1 000 people)
- If you inject this medicine too often at the same place, the skin may shrink (lipoatrophy) or thicken (lipohypertrophy).
- Lumps under the skin may also be caused by build-up of a protein called amyloid (cutaneous amyloidosis) if you often inject your insulin at the same place. How often this occurs is not known.
- This medicine may not work very well if you inject into a lumpy, shrunken or thickened area.
- Change the injection site with each injection to help prevent these skin changes.

Other side effects include:
Common (may affect up to 1 in 10 people)
- Skin problems where the injection is given such as bruising, bleeding, pain or discomfort, redness, swelling, itching.
- Peripheral oedema (swelling especially of the ankles and feet due to fluid retention).

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 Awiqli

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

Before first use
Store in a refrigerator (2 °C - 8 °C).
Do not freeze. Keep away from the freezing element.
Keep the cap on the pen in order to protect it from light.

After first opening or if carried as a spare
You can carry your Awiqli pre-filled pen (FlexTouch) with you and keep it at room temperature (below 30 °C) or in a refrigerator (2 °C - 8 °C) for up to 12 weeks.

Always keep the cap on the pen when you are not using it in order to protect it from light.

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 Awiqli contains
– The active substance is insulin icodec. Each mL of solution contains 700 units of insulin icodec. Each pre-filled pen contains 700, 1 050 or 2 100 units of insulin icodec in 1, 1.5 or 3 mL solution, respectively.
– The other ingredients are glycerol, metacresol, phenol, zinc acetate, sodium chloride, hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections (see section 2).

What Awiqli looks like and contents of the pack
Awiqli is presented as a clear and colourless solution for injection in a pre-filled pen.

The outer packaging is in green with the strength ‘700 units/mL’ indicated in a yellow-coloured box. The pen body is in green while the pen label is in darker green with a yellow box highlighting the formulation strength.

Pack sizes
- Pack size of 1 pre-filled pen of 1 mL (without needles).
- Pack size of 1 pre-filled pen of 1 mL (with 9 or 14 disposable NovoFine Plus needles).
- Pack size of 1 pre-filled pen of 1.5 mL (without needles).
- Pack size of 1 pre-filled pen of 1.5 mL (with 13 or 14 disposable NovoFine Plus needles).
- Multipack of 2 pre-filled pens of 1.5 mL (with 26 or 28 disposable NovoFine Plus needles).
- Pack size of 1 pre-filled pen of 3 mL (without needles).
- Pack size of 2 pre-filled pens of 3 mL (without needles).
- Pack size of 1 pre-filled pen of 3 mL (with 13 or 14 disposable NovoFine Plus needles).
- Multipack of 2 pre-filled pens of 3 mL (with 26 or 28 disposable NovoFine Plus needles).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Novo Nordisk A/S
Novo Alle 1
DK-2880 Bagsvaerd
Denmark

This leaflet was last revised in

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

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

General effects from diabetes treatment
Too low blood sugar (hypoglycaemia)
This may happen if you:
- drink alcohol
- use too much insulin
- exercise more than usual
- eat too little or miss a meal.

Warning signs of too low blood sugar - these may come on suddenly:
- headache
- fast heartbeat
- feeling sick or very hungry
- cold sweat or cool pale skin
- short-lasting changes in your sight
- tremor or feeling nervous or worried
- feeling unusually tired, weak and sleepy
- slurred speech, feeling confused, difficulty in concentrating.

What to do if you get too low blood sugar:
- Eat glucose tablets or another high sugar snack, like sweets, biscuits or fruit juice (always carry glucose tablets or a high sugar snack, just in case).
- Measure your blood sugar if possible and rest. You may need to measure your blood sugar more than once. This is because with basal insulins like Awiqli, the increase in blood sugar may be delayed.
- Then wait until the signs of too low blood sugar have gone or when your blood sugar level has settled. Then carry on with your insulin as usual.
- If you have type 1 diabetes and experience multiple episodes of too low blood sugar, you should consult your doctor.

What others need to do if you pass out
Tell everyone you spend time with that you have diabetes. Tell them what could happen if your blood sugar gets too low, including the risk of passing out.

Let them know that if you pass out, they must:
- turn you on your side
- get medical help straight away
- **not** give you any food or drink because you may choke.

You may recover more quickly from passing out with administration of glucagon. This can only be given by someone who knows how to use it.
- If you are given glucagon, you will need sugar or a sugary snack as soon as you come round.
- If you do not respond to glucagon, you will have to be treated in a hospital.

If severe low blood sugar is not treated over time, it can cause brain damage. This can be short or long-lasting. It may even cause death.

Talk to your doctor if:
- your blood sugar got so low that you passed out
- you have used glucagon
- you have had too low blood sugar a few times recently.

This is because the dosing of your insulin injections, food or exercise may need to be changed.

Too high blood sugar (hyperglycaemia)
This may happen if you:
- drink alcohol
- get an infection or a fever
- have not used enough insulin
- eat more or exercise less than usual
- keep using less insulin than you need
- forget to use your insulin or stop using insulin without talking to your doctor.

Warning signs of too high blood sugar - these normally appear gradually:
- feeling thirsty
- flushed or dry skin
- losing your appetite
- feeling sleepy or tired
- passing water more often
- dry mouth or fruity (acetone) breath
- feeling or being sick (nausea or vomiting).

These may be signs of a very serious condition called ketoacidosis. This is a build-up of acid in the blood because the body is breaking down fat instead of sugar. If not treated, this could lead to diabetic coma and eventually death.

What to do if you get too high blood sugar:
- test your blood sugar level.
- test your urine or blood for ketones.
- get medical help straight away.

Instructions for use

Before you begin using your needle and Awiqli pen, **always read these instructions carefully,** and talk to your doctor, nurse or pharmacist about how to inject Awiqli correctly.

Awiqli pen is a pre-filled disposable pen containing insulin icodec 700 units/mL. You can inject from 10 to 700 units in a single once-weekly injection.

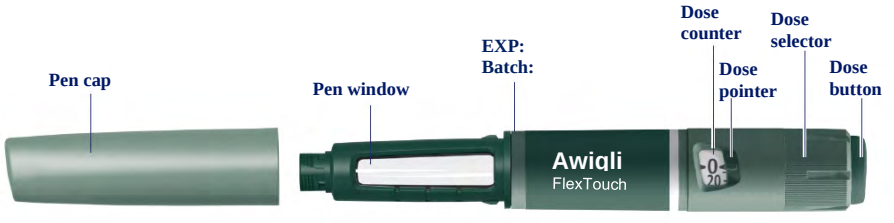
Always start by checking your pen label to make sure that it contains Awiqli 700 units/mL.

Your pen is designed to be used with NovoFine Plus, NovoFine or NovoTwist disposable needles up to a length of 8 mm.

Once-weekly injection

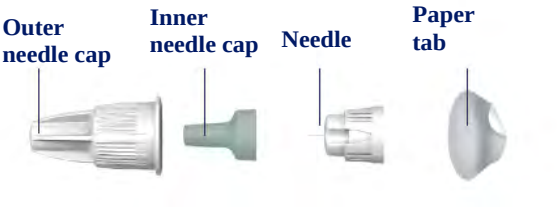
Awiqli pen

Please note: Your pen may differ in size from the pen shown in the picture. These instructions apply to all Awiqli pens.



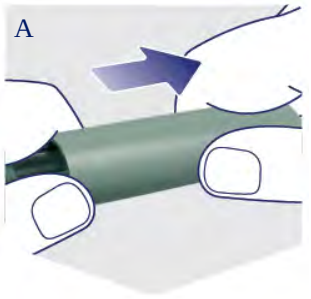
About your needles
Always use a new needle for each injection. Check the flow as described in 'Step 2' and use a new needle for each injection. Always remove the needle after each use.

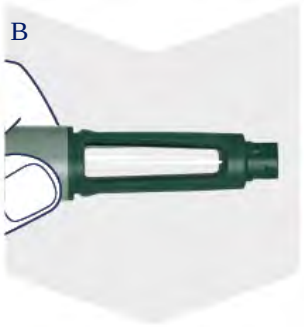
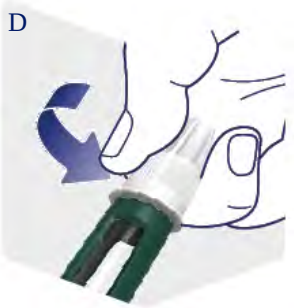
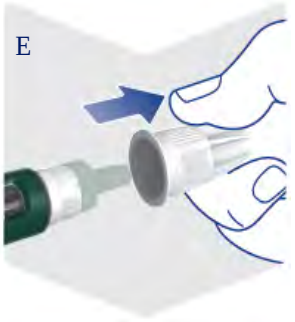
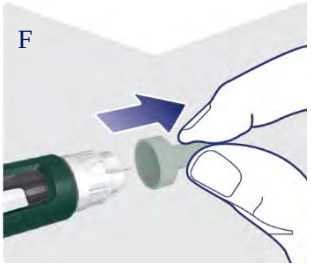
NovoFine Plus Needle (example)



Step 1 Prepare your pen with a new needle

- **Check the name and concentration on the pen label** to make sure that your pen contains insulin icodec 700 units/mL.
- Pull off the pen cap. See Figure A.



• **Always check that the insulin in your pen is clear and colourless.** • Look through the pen window. If the insulin looks cloudy or contains particles, do not use the pen. See Figure B.	B 
• **Always use a new needle for each injection.** • Check the paper tab and outer needle cap for damages. If you see any damage, this could affect sterility. Throw out the needle and use a new one. • Take a new needle and tear off the paper tab. • **Do not attach a new needle to your pen until you are ready to give your injection.** See Figure C.	C 
• **Push the needle straight onto the pen. Turn until it is on tight.** See Figure D. • **The needle is covered by two caps. You must remove both caps.** If you forget to remove both caps, you will not inject any Awiqli.	D 
• Pull off the outer needle cap and keep it for later. You will need it to safely remove the needle from the pen after the injection. See Figure E. • **Pull off the inner needle cap and throw it away.** See Figure F. • A drop of Awiqli may appear at the needle tip. This is normal, but you must still check the Awiqli flow before each injection. See '**Step 2'**. • **Never use a bent or damaged needle.**	E  F 
Step 2 Check the flow before each injection	

- **Always check the flow before each injection.** This helps you to ensure you will get your full Awiqli dose.
- Turn the dose selector clockwise until you see the first mark (10 units) on the dose counter. See Figure G.
- Make sure that the mark lines up with the dose pointer. See Figure H.

G

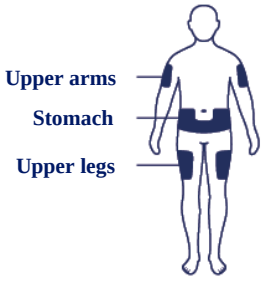
H

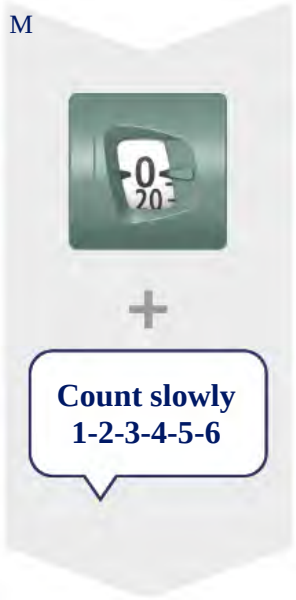
- Hold the pen with the needle pointing up.
- **Press and hold in the dose button until the dose counter shows 0.** The 0 must line up with the dose pointer.
- A drop of Awiqli should appear at the needle tip. This drop indicates that your pen is ready for use. See Figure I.
- **If a drop does not appear, check the flow again.** This should only be done six times in total.
- **If there is still no drop,** you might have a blocked needle. Change the needle as described in '**Step 5' and 'Step 1'.**
- Then check the flow once more.
- **Do not use the pen** if a drop of Awiqli still does not appear.

I

Step 3 Set your dose

- Check that the dose pointer is set at 0. See Figure J.

• Turn the dose selector to select the number of units you need to inject as directed by your nurse or doctor. The dose counter shows the dose dialled in units. • **Make sure you select your intended dose.**	J 
• The units shown in the dose counter will guide you to your dose. The dose can be increased by **10 units** at a time. • You will hear a 'click' every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear. • If you select a wrong dose, you can turn the dose selector forwards or backwards to the correct dose.	
• When your dose lines up with the dose pointer, you have selected your dose. **Make sure you select your intended dose.** • The pictures show examples of how to choose your dose correctly. See Figure K. • If the dose counter stops before you reach your prescribed dose, see the section **'Do you have enough Awiqli?'** below these instructions.	K **70 units selected** **270 units selected** 
Choose your injection site • Choose an injection site on your stomach (keep a 5 cm distance from your belly button), upper legs, or upper arms. • You may inject in the same body area each week, but make sure it is not in the same spot that was used for your last injection.	
Step 4 Inject your dose	
• Fully insert the needle into your skin. See Figure L. • Make sure you can see the dose counter. **Do not cover the dose counter or touch it with your fingers**. This could stop the injection.	

	L 
• **Press and hold down the dose button until the dose counter shows -0-.** • **Continue pressing the dose button with the needle in your skin and slowly count to 6.** The -0- must line up with the dose pointer. See Figure M. You may hear or feel a click when the dose counter returns to -0-.	M 
• Remove the needle from your skin, you can then release the dose button. See Figure N. • If the needle is removed earlier, a stream of Awiqli might come from the needle tip and the full dose will not be delivered. • If blood appears at the injection site, press lightly on the area to stop the bleeding. • You may see a drop of Awiqli at the needle tip after injecting. This is normal and does not affect your dose.	N 
Step 5 After your injection	

• Carefully insert the needle tip into the outer needle cap on a flat surface without touching the needle or the outer needle cap. See Figure O. • Once the needle is covered, carefully push the outer needle cap completely on.	O 
• Unscrew the needle and dispose of it carefully as instructed by your doctor, nurse, pharmacist or local authorities. See Figure P. • Never try to put the inner needle cap back on the needle. You may stick yourself with the needle. • **Always remove and dispose of the needle immediately after each injection** to prevent contamination, infection, blocked needles and inaccurate dosing. • Never store your pen with the needle attached.	P 
• **Put the pen cap on** your pen after each use to protect Awiqli from light. See Figure Q. • When the pen is empty, dispose of the pen without a needle on as instructed by your doctor, nurse, pharmacist or local authorities. • The leaflet and the empty carton can be disposed of in your household waste.	Q 

Do you have enough Awiqli?

- If the dose counter stops before you reach your dose, there is not enough Awiqli left for a full dose. The number shown in the dose counter is the number of units left in your pen.
- **If you need more Awiqli than what is left in your pen,** you can split your dose between two pens. Be sure that you calculate correctly if you are splitting your dose. If you are in doubt, dispose of the used pen and take the full dose with a new pen.
- **If you split the dose incorrectly, you will inject too little or too much Awiqli, which can lead to too high or too low blood sugar level.**

Important information

- **Needles are for single-use only. Never reuse your needles.** This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.
- **Treat your pen with care.** Rough handling or misuse may cause inaccurate dosing, which can lead to too high or too low blood sugar level.
- **Caregivers must be very careful when handling needles** to prevent accidental needle stick injuries and infection.
- **Do not use this pen without help if you have poor eyesight and cannot follow these instructions.** Get help from a person with good eyesight who is trained to use the Awiqli pen.
- **Always keep pen, and needles out of sight and reach of others, especially children.**
- **Inject Awiqli once weekly.**
- **Use your Awiqli as prescribed. If you do not use your Awiqli as prescribed, this can lead to too high or too low blood sugar level.**
- **If you use more than one type of injectable medicine, it is very important to check the name and concentration** of your pen label before use.
- **Never share** your pen or your needles with other people.

Caring for your pen

- Do not freeze Awiqli. Do not use Awiqli if it has been frozen. Dispose of the pen.
- Do not drop your pen or knock it against hard surfaces.
- Avoid exposing Awiqli to direct sunlight.
- Keep Awiqli away from heat, microwaves and out of the light.
- Do not try to repair your pen or pull it apart.
- Do not expose your pen to dust, dirt, or liquid.
- Do not wash, soak, or lubricate your pen. It may be cleaned with a mild detergent on a moistened cloth.
- See the back of this leaflet to read the storage conditions for your pen.