1. NAME OF THE MEDICINAL PRODUCT

Awiqli®

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

Patient Guide
The marketing of Awiqli is subject to a risk management plan (RMP) including a 'Patient Guide'. The 'PatientGuide', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the guide before starting treatment.

4.1 Therapeutic indications

Treatment of Type 2 Diabetes in adults.
Treatment of Type 1 Diabetes in adults, in conjunction with a bolus insulin, where daily basal insulin injections are not suitable

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
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 of the administered product should be clearly recorded. It is recommended to record the batch number as well.

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 who are/have been treated with other once-weekly injectable antidiabetic medicines should pay special attention, as the selection of the prescribed dose of Awiqli differs from that of other once-weekly injectable antidiabetic medicines. Patients must visually verify the dialled units on the dose counter of the pre-filled pen and never select the maximum single dose (700U) unless this is their prescribed dose. 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		Injection site reaction		

administration site conditions		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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

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.

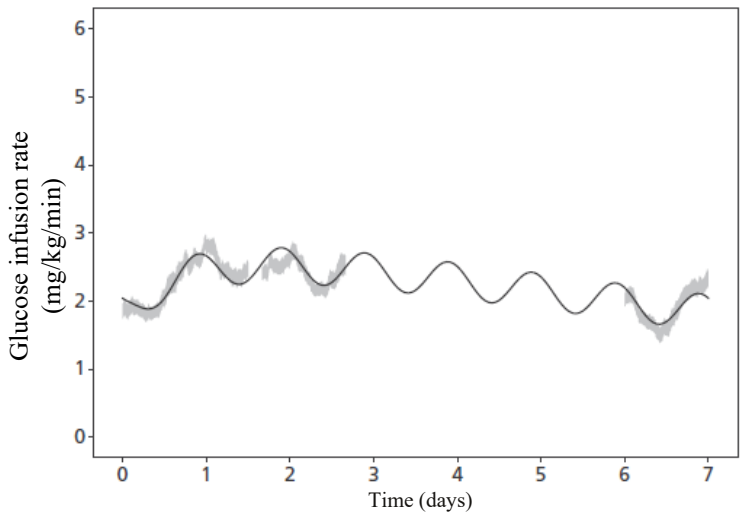
Mechanism of action

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}				
< 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)	<0.01 (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}		
< 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}		
< 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

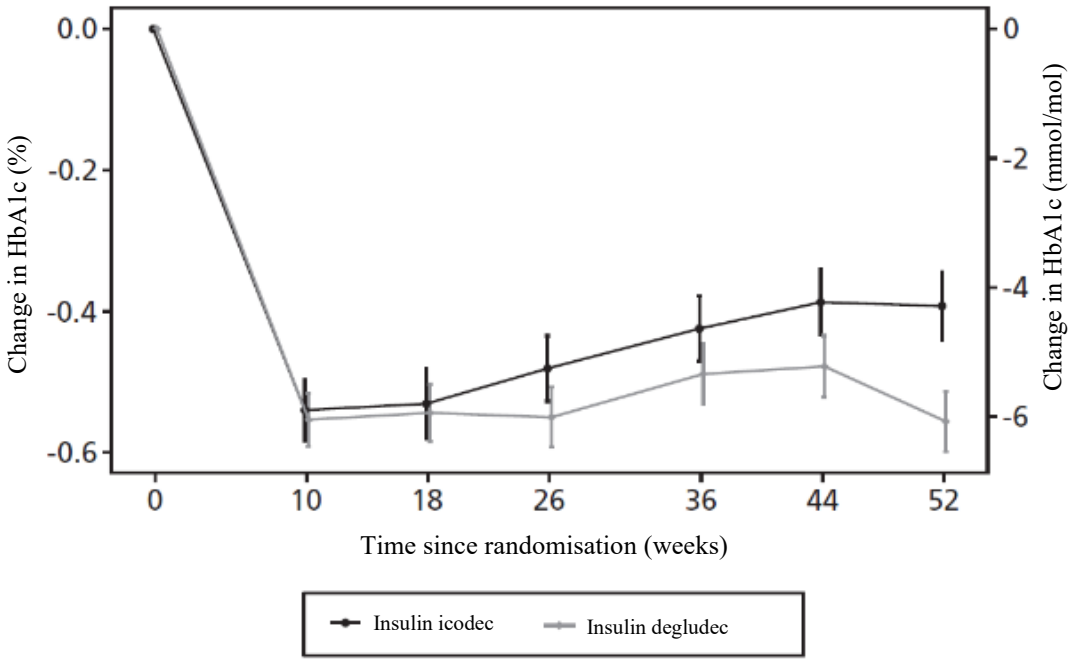
basal insulin treatment (either twice daily/insulin glargine 300 units/mL or once daily) and HbA_{1c} (either < 8% or ≥ 8%) at screening (Table 6).

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} (%)		
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

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
Phenol

Sodium chlorid
Metacresol
Zinc acetate
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

The expiry date of the product is indicated on the packaging materials.

Shelf life after first opening of the pen or when carried as a spare
After first opening or if 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.

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.

Awiqli pre-filled pen containing 2,100 units of insulin icodec in 3 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.

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. REGISTRATION HOLDER

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9. REGISTRATION NUMBER

179-81-38245

Revised in January 2026.