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 (see Section 5.1 Pharmacodynamic Properties).

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

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 (see section 5.1 Pharmacodynamic Properties, Clinical Trials).

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, other applicable adjustments, e.g. glucose intake or changes to other glucose lowering medication, may be considered.

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 Special Warnings and Precautions for Use).

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 pre-filled pens. The dose window shows the number of units of Awiqli to be injected.

Awiqli must not be drawn from the cartridge of the pre-filled pen into a syringe (see Section 4.4 Special Warnings and Precautions for Use).

For further information before administration see Section 6.6 Special Precautions for Disposal.

Dosage Adjustment

Missed dose
If a dose is missed, it is recommended that it is administered as soon as possible. If it is still within 3 days of the missed dose, the patient can then resume their once-weekly dosing schedule.

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 when the missed dose was administered.

If the patient wishes to go back to their original dosing day, they may extend the time between subsequent doses by 1 to 3 days.

Patients then must be instructed to continue their dosing once-weekly. Monitoring of fasting plasma glucose is recommended.

Changing the dosing schedule
The day of once-weekly administration can be changed if necessary, as long as the time between two doses is at least 4 days. After selecting a new dosing day, once-weekly dosing should be continued.

Initiation of Awiqli in basal insulin-naïve patients

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 with type 1 diabetes mellitus
Awiqli is to be used once-weekly with bolus insulin and requires subsequent individual once-weekly dose adjustments.

Starting dose in patients switching from once- or twice-daily basal insulin therapy to Awiqli

The first once-weekly dose of Awiqli should be taken 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 7 times the total daily basal dose of the previous basal insulin. Subsequent doses of Awiqli can be titrated based on the patient's metabolic needs, blood glucose monitoring results, and glycaemic control goal. See Table 1.

Table 1 Standard dosing example

Previous total daily dose of once- or twice-daily basal insulin (units)	**Awiqli once-weekly dose**	
	Week 1 (units)	Week 2 onwards
10	70	Titrate based on patient's requirements

Awiqli is available in 3 different presentations of FlexTouch® pens: 700 U, 1050 U and 2100 U. The choice of pen presentation should be based on the weekly dose of insulin a patient requires (see Table 2). Patients naïve to insulin, starting on 70 IU a week (10 IU/day equivalent) could use the 700 U pen. Patients on doses higher than 160 IU a week (approximately 23 IU/day equivalent) could use the 1050 U or 2100 U dose pen.

Table 2 Awiqli dose and pen presentation options

Weekly dose [daily dose equivalent][a] (IU)	**Pen presentations**	**Number of weeks depending on weekly dose[b]**
70 - 160 [10 - 23]	700 U	8 - 4, respectively
80 - 250 [11 - 36]	1050 U	11 - 4, respectively
160 - 510 [23 - 73][c]	2100 U	12 - 4, respectively

[a] Takes into account 10 U priming shots before each injection.
[b] After first opening, or if carried as a spare, Awiqli can be used for 12 weeks before discarding any remaining insulin (see Section 6.4 Special Precautions for Storage)
[c] Patients on doses higher than 510 IU a week (approximately 73 IU/day equivalent), will have less than 4 weekly doses available in the 2100 U dose pen.

For patients requiring an initial one-time dose increase (optional)

Depending on the patient's glycaemic control, hypoglycaemia history and treatment goals at the initiation of the switch, a one-time 50% additional dose of Awiqli may be administered, (i.e., the initial dose would then be, 1.5x the previous daily basal insulin dose x 7, as illustrated in Table 3), rounded to the nearest 10 units (see Table 3). When assessing the potential need for the one-time additional dose, the risks of hypoglycaemic events (including medication errors) should be weighed against the temporary worsening of glycaemic control (hyperglycaemia) (see Section 4.4 Special Warnings and Precautions for Use).

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

The third and subsequent once-weekly dose 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.

Close glucose monitoring is recommended during the switch and in the following weeks. In patients who initially receive an additionally increased dose of insulin icodec, medication errors may occur during the subsequent injection in week 2 (see Section 4.4 Special Warnings and Precautions for Use). Doses and timing of concurrent bolus insulin products or other concomitant antidiabetic treatment may need to be adjusted.

Table 3 Guidance if an initial dose of 1.5x is required of Awiqli in week 1 (optional when switching from once- or twice-daily basal insulin)

Previous total daily dose of once- or twice-daily basal insulin (units)	Recommended Awiqli once-weekly dose[a] (if optional initial dose of 1.5x required)	
	Week 1[b] (units)	Week 2[c] (units)
10	110	70
11	120	80

Previous total daily dose of once- or twice-daily basal insulin (units)	Recommended Awiqli once-weekly dose[a] (if optional initial dose of 1.5x required)	
	Week 1[b] (units)	Week 2[c] (units)
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] previous total daily basal insulin dose multiplied by 7 + 50% one-time additional dose, if appropriate
[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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of Excipients.

4.4 Special Warnings and Precautions for Use

Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see Sections 4.5 Interactions with Other Medicines, 4.8 Adverse Effects and 4.9 Overdose).

The risk of hypoglycaemia with insulin icodec corresponds to the weekly profile of its glucose-lowering effect, which reaches its maximum approximately 2-4 days after each weekly injection (see Section 4.8 Adverse Effects, and Pharmacodynamic effects in Section 5.1 Pharmacodynamic Properties). Patients who initially receive a one-time additional dose of insulin icodec (see Section 4.2 Dose and Method of Administration) should be appropriately informed and advised regarding potential medication errors during the subsequent injection in week 2.

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, as usual warning symptoms may disappear or be disregarded in patients with long-standing diabetes.

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 Interaction with Other Medicines).

For type 1 diabetes, patients treated with insulin icodec, higher risk of hypoglycaemia could occur. If a type 1 diabetes patient experiences recurrent hypoglycaemia, they should consult their healthcare provider to consider treatment adjustments or other treatment options.

The safety of insulin icodec in patients with hypoglycaemia unawareness has not been established. Therefore, the treatment with insulin icodec is not recommended in such patients.

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.

Hypersensitivity

Allergic reactions may occur with all insulin preparations. Immediate-type allergic reactions to either insulin itself or the excipients may potentially be life-threatening. In the clinical trials with insulin icodec, hypersensitivity reactions have been reported in patients treated with insulin icodec (see Section 4.8 Adverse Effects).

Switch between other insulins and insulin icodec

Switching a patient between another type, brand or manufacturer of insulin and insulin icodec should be done under medical supervision and may result in the need for a change in dosage (see Section 4.2 Dose and Method of Administration).

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 Dose and Method of Administration and 4.9 Overdose).

Patients who are uncertain about the correct dose must be instructed to consult their healthcare professional 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 (see Section 6.6 Special Precautions for Disposal).

Insulin antibodies
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.

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.

Use in hepatic impairment
Awiqli can be used in hepatic impaired patients. In patients with hepatic impairment, more frequent glucose monitoring is recommended (see Section 5.2 Pharmacokinetic Properties).

Use in renal impairment
Awiqli can be used in renal impaired patients. In patients with renal impairment, more frequent glucose monitoring is recommended (see Section 5.2 Pharmacokinetic Properties).

Use in elderly
Awiqli can be used in elderly patients. More frequent glucose monitoring is recommended. Therapeutic experience in patients ≥ 75 years of age is limited (see Section 5.2 Pharmacokinetic Properties).

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

Effects on laboratory tests
No data available.

4.5 Interaction with Other Medicines and Other Form of Interactions

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

The following substances may **reduce** the insulin requirement
Antidiabetic medicinal products, GLP-1 receptor agonists, 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

Effects on fertility
Fertility was unaffected in male and female rats with daily subcutaneous administration of insulin icodec at doses up to 100 and 60nmol/kg/day in the respective sexes (yielding average plasma concentrations approximately 4.3 and 2.6 times higher than in patients treated at 230 U/week).

Use in pregnancy
Pregnancy Category: B3

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

No adverse effects on embryofoetal development were observed with insulin icodec in rats at daily subcutaneous doses of up to 60 nmol/kg/day (yielding an average plasma concentration 1.5 times higher than in patients treated at 230 U/week). In rabbits, abortions occurred at ≥18 nmol/kg/day (relative exposure, 1.7) and increased post-implantation loss was observed at 24 nmol/kg/day (relative exposure, 1.9). Insulin icodec did not cause malformations in either species. The adverse effects on embryofoetal development observed in rabbits are considered to be secondary to maternal hypoglycaemia, and not to reflect a direct effect of insulin icodec on the developing embryo/foetus. Accordingly, limited clinical relevance is seen.
Because of lack of experience during pregnancy, women of childbearing potential should be advised to discontinue insulin icodec, if they wish to become pregnant.

Use in lactation
There is no clinical experience with use of insulin icodec during breast-feeding. Excretion of insulin icodec in human milk has not been specifically studied, but is expected from data for other insulins and from the detection of insulin icodec in pups of treated lactating rats. While exposure in suckling rat pups was found to be low and not at pharmacologically significant levels, a risk to the infant/child cannot be excluded. Insulin icodec should be used with caution in a breast-feeding woman.

4.7 Effects on Ability to Drive and Use Machines

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

Patients 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 Adverse Effects

Summary of the safety profile
The overall safety profile of insulin icodec is based on 6 phase 3 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.

The most frequently reported adverse reaction during clinical trials with insulin icodec is hypoglycaemia (see Sections 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties).

Tabulated list of adverse reactions
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 4 Tabulated list of adverse reactions

MedDRA system organ classes	Very common	Common	Uncommon
Immune system disorders			Hypersensitivity[a]
Metabolism and nutrition disorders	Hypoglycaemia		
General disorders and administration site conditions		Injection site reaction[b] Peripheral oedema[c]	

[a] Grouped term covering adverse events related to hypersensitivity such as Preferred Terms: Urticaria, Lip swelling and Swelling face

[b] Grouped term covering adverse events related to injection site reactions such as Preferred Terms: Injection site reaction, Injection site erythema, Injection site pain, Injection site bruising, Injection site hypersensitivity, Injection site pruritus, Injection site swelling, Injection site urticaria, Injection site mass, Application site bruise, Application site pruritus

[c] Grouped term covering adverse events related to peripheral oedema such as Preferred Terms: Oedema peripheral and Peripheral swelling

Hypoglycaemia

Hypoglycaemia is the most commonly observed adverse drug reaction in patients using insulin icodec (see Sections 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties).

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 3.0 mmol/L (54 mg/dL).

The proportion of patients reporting severe or clinically significant hypoglycaemic episodes with insulin icodec vs daily basal insulin was 8.9%-11.8% vs 6.1%-10.6% in insulin naïve type 2 diabetes mellitus patients (ONWARDS 1, 3 and 5), 14% vs 7% in type 2 diabetes mellitus patients treated with basal insulin (ONWARDS 2), 51% vs 56% in type 2 diabetes mellitus patients previously on basal-bolus insulin regimen (ONWARDS 4) and 85% vs 76 % in type 1 diabetes mellitus patients (ONWARDS 6). Across ONWARDS trials, most hypoglycaemic episodes were observed in accordance with the glucose-lowering profile on days 2-4 after the weekly administration (see 5.1 Pharmacodynamic Properties).

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.

In a post hoc analysis of two phase 2 trials evaluating insulin icodec and glargine U100 in insulin naïve and experienced T2D patients, based on CGM data, the duration of hypoglycaemic episodes was similar across the different treatment arms and similar results were seen for the nocturnal period.

Insulin antibodies

During the 26-week treatment periods with anti-drug antibody (ADA) sampling conducted up to 31 weeks in three phase 3 clinical trials in adults with type 2 diabetes mellitus, between 1.6% and 31.5% of insulin icodec-treated patients were positive at baseline and between 70.2% and 79.0% were positive for anti-insulin icodec antibodies at least once during the study.

In one phase 3 trial in adults with type 1 diabetes mellitus with ADA sampling up to 57 weeks, the ADA positive rate was 50.2% at baseline and 80.6% any time after baseline.

There was no identified clinically significant effect of anti-insulin icodec antibodies on pharmacokinetics, effectiveness, or safety of insulin icodec in any of the phase 3 trials.

When interpreting differences in the incidence of antibodies against insulin icodec compared to antibodies against other products from previous studies, it should be considered that the detection and quantification of antibody formation depend on the sensitivity and specificity of the respective assay and can be influenced by additional factors (such as the timing of sample collection, concomitant medication, and comorbidities), which may vary.

Other special populations

Based on results from clinical trials, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population (see Section 5.1 Pharmacodynamic Properties).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

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 dosing guidance, continues to be taken after the first injection (see Section 4.4 Special Warnings and Precautions for Use).

Double and triple of normal dose of insulin icodec has been investigated in a clinical trial, and did not lead to increased risk of hypoglycaemia as compared to insulin glargine, provided that the next weekly dose was skipped. (See Section 5.1 Pharmacodynamic Properties).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action

Insulin icodec binds to the human insulin receptor, resulting in the same pharmacological effects as human insulin.

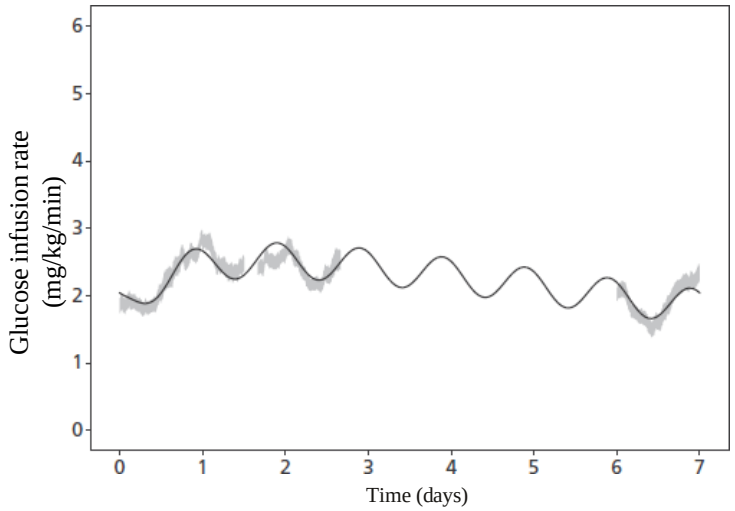
The primary action of insulin, including insulin icodec, is to regulate glucose metabolism. Insulin and its analogues lower blood glucose by activating specific insulin receptors to stimulate peripheral glucose uptake, especially by skeletal muscle and fat as well as to inhibit hepatic glucose production.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

Insulin icodec is a basal insulin. The extended half-life of insulin icodec is mainly due to a strong but reversible binding to albumin. Thereby, a depot of essentially inactive insulin icodec is formed in the circulation and in the interstitial compartment, from which insulin icodec is slowly and continuously released.

In addition, insulin icodec clearance is very slow due to reduced insulin receptor binding and reduced enzymatic degradation.

Pharmacodynamic effects

By virtue of its slowly reversible binding to albumin, reduced insulin receptor binding and clearance, insulin icodec produces an evenly distributed glucose-lowering effect across the dosing interval of one week, and the duration of the glucose-lowering effect covers one week at clinically relevant doses (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

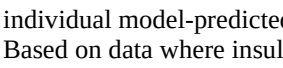


Figure 1: Full-week glucose infusion rate profile of insulin icodec at steady-state in type 2 diabetes

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.

Overdosing has been studied in a clinical trial comparing a double or triple dose of insulin icodec to a double or triple dose of insulin glargine (100 units/mL). No increase in overall risk or prolonged duration of hypoglycaemia was observed with insulin icodec compared to insulin glargine, provided that the next weekly dose was skipped. During the treatment periods, there were no severe hypoglycaemic episodes (level 3). During hypoglycaemia induced by double or triple insulin doses, comparable symptomatic and moderately greater hormonal counter regulatory responses were elicited by insulin icodec compared to insulin glargine.

Clinical trials

The safety and efficacy of insulin icodec were evaluated in six multinational, randomised, active-controlled, open-label or blinded, parallel-group phase 3 clinical trials of 26 or 52 weeks duration (ONWARDS 1-6). The trials exposed 2,170 patients to insulin icodec (1,880 in type 2 diabetes mellitus and 290 in type 1 diabetes mellitus). A treat-to-target approach was followed in all trials except ONWARDS 5, which was designed to mimic a clinical practice setting where insulin icodec was used together with a dosing guide application. In ONWARDS 1-4 and 6, 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 effect of insulin icodec was tested in insulin-naïve patients (insulin initiation in type 2 diabetes mellitus, Tables 5 and 6), in patients previously treated with basal insulin only (insulin intensification in type 2 diabetes mellitus, Table 7), in patients previously treated with basal-bolus regimen (insulin intensification in type 2 diabetes mellitus, Table 8) and in patients with type 1 diabetes mellitus (Table 9).

The reduction in HbA_{1c} from baseline to end of trial was confirmed to be non-inferior in all 6 trials to daily basal insulins. The superiority of insulin icodec over daily basal insulins in reducing HbA_{1c} was shown in four trials in type 2 diabetes mellitus. 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).

Patients with type 2 diabetes mellitus

In three trials involving insulin-naïve patients with type 2 diabetes mellitus (ONWARDS 1, 3 and 5), insulin icodec demonstrated superior glycaemic control (HbA_{1c}) compared to daily basal insulins (Tables 5 and 6). In type 2 diabetes mellitus patients previously treated with basal insulin only (ONWARDS 2), insulin icodec also demonstrated superior glycaemic control (HbA_{1c}) compared to insulin degludec (Table 7).

Results from all clinical trials in type 2 diabetes patients demonstrated that the rate of confirmed hypoglycaemia was not statistically significantly different in patients treated with

insulin icodec compared to patients treated with insulin degludec or insulin glargine (Tables 5, 6, 7, 8).

Proportion of patients achieving HbA_{1c} < 7% without severe or clinically significant hypoglycaemia

In the 4 trials with insulin-naïve patients and patients previously treated with basal insulin only, 36.7% to 52.6% of patients treated with insulin icodec achieved HbA_{1c} < 7% without severe (level 3) or clinically significant (level 2) hypoglycaemia in the prior 12 weeks of planned treatment period. The proportion ranged from 26.8% to 42.6% in patients treated with insulin degludec or insulin glargine (Tables 5, 6, 7).

Table 5 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} (%)				
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]*		*-0.19 [-0.36; -0.03]*	
Patients (%) achieving HbA_{1c}				
< 7%*	56.83	41.64	57.57	45.44
Estimated odds ratio	*1.85 [1.29; 2.64]*[a]		*1.63 [1.24; 2.14]*[a]	
< 7% without level 2 or 3 hypoglycaemia*	52.13	39.86	52.56	42.58
	26 weeks of treatment – ONWARDS 3		52 weeks of treatment – ONWARDS 1	
	Insulin icodec	**Insulin degludec**	**Insulin icodec**	**Insulin glargine 100 units/mL**
Estimated odds ratio	*1.64 [1.16; 2.33]*[a]		*1.49 [1.15; 1.94]*[a]	
Fasting Plasma Glucose (mmol/L)				
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]*		*-0.01 [-0.27; 0.24]*	
Time in Range (3.9-10.0 mmol/L) (%)				
Weeks 48-52			71.94	66.90
Estimated difference			*4.27 [1.92; 6.62]*[b]	
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]*		*1.67 [0.99; 2.84]*	

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Level 3	0 (0)	0.1 (0.7)	<0.01 (0.2)	0 (0.6)
Level 2 or level 3	0.31 (8.9)	0.15 (6.1)	0.3 (9.8)	0.16 (10.6)
Estimated rate ratio	*1.82 [0.87; 3.80]*		*1.64 [0.98; 2.75]*	

PYE = patient years of exposure
* Least Squares (LS) mean
[a] 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
[b] 4.27% corresponds to approximately 61 minutes more spent within range per day.

Table 6 Results from open-label clinical trial in insulin naïve adults with type 2 diabetes mellitus – ONWARDS 5

	52 weeks of treatment	
	Insulin icodec with dosing guidance application	**Daily basal insulins****
N (Full Analysis Set)	542	543
HbA_{1c} (%)		
End of trial*	7.24	7.61
Change from baseline*	-1.68	-1.31
Estimated difference	*-0.38 [-0.66; -0.09]*	
Patients (%) achieving HbA_{1c}		
< 7%*	46.76	34.65
Estimated odds ratio	*1.66 [1.24; 2.21][a]*	
< 7% without level 2 or 3 hypoglycaemia*	40.53[b]	31.61
Estimated odds ratio	*1.47 [1.13; 1.92][a]*	
Rate of hypoglycaemia per PYE (percentage of patients)		
Level 2	0.19 (11.8)	0.14 (7.8)
Estimated rate ratio	*1.23 [0.77; 1.98]*	
	52 weeks of treatment	
	Insulin icodec with dosing guidance application	**Daily basal insulins****
Level 3	0 (0)	0 (0.7)
Level 2 or level 3	0.19 (11.8)	0.14 (8.4)
Estimated rate ratio	*1.17 [0.73; 1.86]*	
Patient reported outcomes		
DTSQs sum score – change from baseline*,[b]	4.68	3.90
Estimated difference	*0.78 [0.10; 1.47]*	
TRIM-D estimated score*,[c]	90.42	87.37
Estimated difference	*3.04 [1.28; 4.81]*	

PYE = patient years of exposure
* Least Squares (LS) mean
** daily basal insulins include insulin degludec and insulin glargine (100 units/mL and 300 units/mL)
[a] higher odds of achieving HbA_{1c} target without level 3 or level 2 hypoglycaemia in the prior 12 weeks in

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patients treated with insulin icodec

[b] the DTSQs domain score in total treatment satisfaction is calculated by adding six item scores. The total score can range from 0 to 36, with 0 being the lowest and 36 being the highest score in total treatment satisfaction

[c] the TRIM-D compliance domain score, which can range from 0 to 100 with higher score indicating better compliance, was measured at week 52.

Table 7 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} (%)		
End of trial*	7.20	7.42
Change from baseline*	-0.93	-0.71
Estimated difference	*-0.22 [-0.37; -0.08]*	
Patients (%) achieving HbA_{1c}		
< 7%*	40.32	26.49
Estimated odds ratio	*1.88 [1.26; 2.79]*[a]	
< 7% without level 2 or 3 hypoglycaemia*	36.73	26.79
Estimated odds ratio	*1.59 [1.07; 2.36]*[a]	
Fasting Plasma Glucose (mmol/L)		
End of trial*	6.83	6.79
Change from baseline*	-1.58	-1.62
Estimated difference	*0.04 [-0.28; 0.36]*	
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]	
	26 weeks of treatment	
	Insulin icodec	**Insulin degludec**
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]*	
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]*	
Patient reported outcomes		
DTSQs sum score – change from baseline*,[c]	4.22	2.96
Estimated difference	*1.25 [0.41; 2.10]*	

Abbreviations: PYE = patient years of exposure; cfb = change from baseline

* Least Squares (LS) mean

[a] 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

[b] 2.41% corresponds to approximately 35 minutes more spent within range per day

[c] the DTSQs domain score in total treatment satisfaction is calculated by adding six item scores. The score can range from 0 to 36, with 0 being the lowest and 36 being the highest score in total treatment satisfaction.

Table 8 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**
N (Full Analysis Set)	291	291
HbA_{1c} (%)		
End of trial*	7.14	7.12
Change from baseline*	-1.16	-1.18
Estimated difference	*0.02 [-0.11; 0.15]*	
Patients (%) achieving HbA_{1c}		
< 7%*	40.69	45.48
Estimated odds ratio	*0.82 [0.58; 1.17]*	
< 7% without level 2 or 3 hypoglycaemic episodes*	26.48	25.24
Estimated odds ratio	*1.07 [0.73; 1.55]*	
Fasting Plasma Glucose (mmol/L)		
End of trial*	7.67	7.81
Change from baseline*	-1.75	-1.61
Estimated difference	*-0.14 [-0.59; 0.31]*	
Time in Range (3.9-10.0 mmol/L) (%)		
Weeks 22-26	66.88	66.44
Estimated difference	*0.29 [-2.52; 3.09][a]*	
Rate of hypoglycaemia per PYE (percentage of patients)		
Level 2	5.60 (50.9)	5.61 (55.0)
	26 weeks of treatment	
	Insulin icodec	**Insulin glargine 100**
Estimated rate ratio	*0.99 [0.73; 1.34]*	
Level 3	0.04 (1.4)	0.02 (0.7)
Estimated rate ratio	*2.19 [0.20; 24.44]*	
Level 2 or level 3	5.64 (51.5)	5.62 (55.7)
Estimated rate ratio	*0.99 [0.73; 1.33]*	

PYE = patient years of exposure
* Least Squares (LS) mean
[a] 0.29% corresponds to approximately 4 minutes more spent within range per day.

Patients with type 1 diabetes mellitus

In patients with type 1 diabetes mellitus, treatment with insulin icodec demonstrated a non-inferior HbA_{1c} reduction compared to insulin degludec. In this patient population, the rate of hypoglycaemia was statistically significantly higher in patients treated with insulin icodec compared to insulin degludec (Table 9).

Table 9 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} (%)		
End of trial*	7.15	7.10
Change from baseline*	-0.47	-0.51
Estimated difference	*0.05 [-0.13; 0.23]*	
Patients (%) achieving HbA_{1c}		
< 7%*	40.20	45.72
Estimated odds ratio	*0.80 [0.53; 1.19]*	
< 7% without level 2 or 3 hypoglycaemic episodes*	9.55	16.74
Estimated odds ratio	*0.52 [0.33; 0.85]*[a]	
Fasting Plasma Glucose (mmol/L)		
End of trial*	8.91	7.88
Change from baseline*	-0.84	-1.87
Estimated difference	*1.03 [0.48; 1.59]*	
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]	
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]*	
Level 3	0.33 (3.1)	0.12 (3.1)

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	26 weeks of treatment	
	Insulin icodec	**Insulin degludec**
Estimated rate ratio	*2.08 [0.39; 10.96]*	
Level 2 or level 3	19.93 (85.2)	10.37 (76.4)
Estimated rate ratio	*1.89 [1.54; 2.33]*	
Patient reported outcomes		
DTSQs sum score – change from baseline[*,c]	1.97	3.06
Estimated difference	*-1.09 [-1.85; -0.34]*	

Abbreviations: PYE = patient years of exposure
* Least Squares (LS) mean
** unblinded CGM data was captured from a trial in patients with type 1 diabetes mellitus
[a] 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
[b] -2.00% corresponds to approximately 29 minutes less spent within range per day
[c] the DTSQs domain score in total treatment satisfaction is calculated by adding six item scores. The score can range from 0 to 36, with 0 being the lowest and 36 being the highest score in total treatment satisfaction.

Continuous glucose monitoring (CGM)
In an open-label clinical trial (ONWARDS 1), insulin-naïve type 2 diabetes patients treated with once-weekly insulin icodec spent 71.94% time in range (3.9-10 mmol/L) compared to 66.90% with insulin glargine 100 units/mL as measured with blinded CGM. The estimated treatment difference between the two arms was statistically significant at 4.27% [1.92; 6.62], which corresponds to approximately 61 minutes more spent within range per day in the insulin icodec arm. Both groups were assessed at the last four weeks of planned treatment (Table 3).

Patient reported outcomes (PROs)
In type 2 diabetes patients, DTSQs questionnaire was used in one trial involving treatment with basal only in insulin-naïve patients (in conjunction with a dose guidance application) and one trial with patients previously treated with basal insulin only. The results demonstrate that insulin icodec significantly improved total treatment satisfaction compared to daily basal insulins, based on the sum of scores from six items. In addition, the measured compliance domain score of the TRIM-D questionnaire was higher in patients treated with insulin icodec with a dosing guide application compared to daily basal insulins in insulin-naïve type 2 diabetes patients.

In type 1 diabetes patients with a basal-bolus regimen, patients reported an improved treatment satisfaction compared to baseline in both treatment arms. Greater improvement in total treatment satisfaction was reported with insulin degludec than with insulin icodec.

Cardiovascular evaluation
Patients treated with insulin icodec had a similar incidence of major adverse cardiovascular events (MACE) when compared to those treated with a daily basal insulin. The estimated hazard-ratio from the analysis of time to first event adjudication committee (EAC) confirmed occurrence of MACE in the phase 3 pool was HR: 0.84; 95% CI [0.48;1.49] for insulin icodec compared to daily basal insulins.

5.2 Pharmacokinetic Properties

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.

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 subjects).

Distribution
Plasma protein binding by insulin icodec is > 99%, reflecting high affinity for human serum albumin. *In vitro* experiments indicated no clinically relevant displacement of insulin icodec from albumin by palmitate, the most abundant fatty acid in human blood.

Metabolism
Degradation of insulin icodec is similar to that of human insulin; the metabolites present in the serum are considered pharmacologically inactive due to the absence of the A-chain.

Excretion
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.

Gender, age, 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, or between healthy subjects and subjects with renal or hepatic impairment.

5.3 Preclinical Safety Data

Genotoxicity
Insulin icodec is not considered to pose a genotoxic hazard, based on negative results in an assay for bacterial mutagenicity, *in silico* analysis, and considering the nature of the drug molecule.

Carcinogenicity
Standard (2-year) carcinogenicity studies in animals have not been conducted with insulin icodec. No treatment-related increase in tumour incidence and no increase in the incidence/severity of mammary gland hyperplasia were observed with insulin icodec in a 12-month study in rats, involving daily subcutaneous administration at doses up to 60 nmol/kg/day in males and 40 nmol/kg/day in females (yielding average plasma concentrations 3.7 and 2.0 times higher than in patients treated at 230 U/week).

Insulin icodec, like other insulins, has mitogenic as well as metabolic activity. *In vitro* studies show that the balance of mitogenic to metabolic potency of insulin icodec is comparable to that of native human insulin. As well, insulin icodec does not dissociate from the insulin receptor more slowly than insulin (to cause sustained receptor activation, which is associated with increased mitogenic potential).

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.

Substances added to Awiqli may cause degradation of insulin icodec.

Awiqli must not be added to infusion fluids.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

For information on how to store the medicinal product during its shelf life see Section 6.4 Special Precautions for Storage.

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
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.

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

Pack sizes
Awiqli pre-filled pen (FlexTouch) containing 700 units of insulin icodec in 1 mL solution.

- 1 pre-filled pen (with and without disposable NovoFine Plus needles).

Awiqli pre-filled pen (FlexTouch) containing 1,050 units of insulin icodec in 1.5 mL solution.

- 1 pre-filled pen (with and without disposable NovoFine Plus needles).

Awiqli pre-filled pen (FlexTouch) containing 2,100 units of insulin icodec in 3 mL solution.

- 1 pre-filled pen (with and without disposable NovoFine Plus needles).

Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

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.

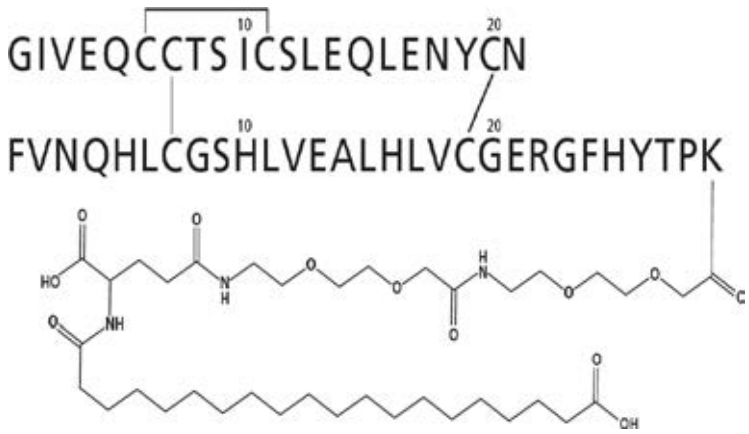
In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet.

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

For detailed instructions for use, see the package leaflet.

6.7 Physicochemical Properties

Chemical structure



CAS number

1188379-43-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

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9. DATE OF FIRST APPROVAL

TBC

10. DATE OF REVISION

N/A

Summary table of changes

Section changed	Summary of new information
N/A	Initial registration