1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults.

4.2 Posology and method of administration

Posology

This medicinal product is a basal insulin for once-weekly subcutaneous administration. It is intended to be taken 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 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).

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.

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.

Missed dose
If a dose is missed, it is recommended that it is administered as soon as possible, ensuring the time between two doses is at least 4 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
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.

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 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 the total daily basal dose multiplied by 7. For the first injection only, a one-time additional 50% Awiqli dose is recommended depending on the patient's glycaemic control and hypoglycaemia history (see Table 1).

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. 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

Previous total daily dose of once- or twice-daily basal insulin (units)	Recommended Awiqli once-weekly dose[a]	
	Week 1[b] (units)	Week 2 (units)[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] previous total daily basal insulin dose multiplied by 7 + 50% one-time additional dose
[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

Special populations
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).

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).

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).

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 pre-filled pens. The dose window shows the number of units of Awiqli to be injected. No dose recalculation is required.

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

To be used as prescribed by doctor only. If experience dizziness or fainting, please consult your doctor immediately.

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).

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.

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).

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).

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).

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

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

Lipodystrophy and cutaneous amyloidosis

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

Eye disorder

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

Avoidance of medication errors

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

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

In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the package leaflet (see section 6.6).

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.

Traceability

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

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.

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

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 insulin icodec, if they wish to become pregnant.

Breast-feeding

There is no clinical experience with use of insulin icodec during breast-feeding. There is no information about excretion of insulin icodec in human milk, or an effect on the breast-fed infant. No metabolic effects are anticipated in the breast-fed newborn/infant.

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

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 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 and 5.1).

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 2: 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

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).

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.

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).

Reporting of suspected adverse reactions

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

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 taken after the first injection (see section 4.4).

Double and triple of normal dose of insulin icodec has been investigated in a clinical trial (see section 5.1).

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

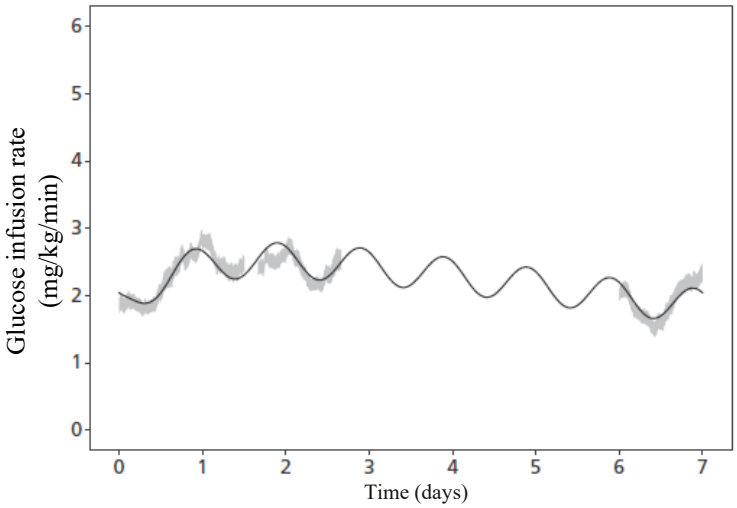
The extended half-life of insulin icodec is mainly due to a strong but reversible binding to albumin. Thereby, a depot of essentially inactive insulin icodec is formed in the circulation and in the interstitial compartment, from which insulin icodec is slowly and continuously released and binds specifically to the insulin receptor leading to an evenly distributed glucose-lowering effect. 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

Insulin icodec is a basal insulin that binds reversibly to albumin, resulting in a depot in the circulation from which insulin icodec is slowly and continuously released. This leads to 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).

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



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).

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 efficacy and safety

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.

The effect of insulin icodec was tested in insulin-naïve patients (insulin initiation in type 2 diabetes mellitus, Tables 3 and 4), in patients previously treated with basal insulin only (insulin intensification in type 2 diabetes mellitus, Table 5), in patients previously treated with basal-bolus regimen (insulin intensification in type 2 diabetes mellitus, Table 6) and in patients with type 1 diabetes mellitus (Table 7).

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 3 and 4). 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 5).

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 3, 4, 5, 6).

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 3, 4, 5).

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} (%)				
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
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 100 PYE (percentage of patients)				
Level 2	31.01 (8.9)	13.44 (5.8)	29.43 (9.8)	15.46 (10.0)
Estimated rate ratio	*2.09 [0.99; 4.41]*		*1.67 [0.99; 2.84]*	
Level 3	0 (0)	1.17 (0.7)	0.21 (0.2)	0.62 (0.6)
Level 2 or level 3	31.01 (8.9)	14.61 (6.1)	29.64 (9.8)	16.08 (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 4 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 100 PYE (percentage of patients)		
Level 2	18.59 (11.8)	13.55 (7.8)
Estimated rate ratio	*1.23 [0.77; 1.98]*	
Level 3	0 (0)	0.89 (0.7)
Level 2 or level 3	18.59 (11.8)	14.45 (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 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 5 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]	
Rate of hypoglycaemia per 100 PYE (percentage of patients)		
Level 2	72.79 (14.1)	26.84 (7.2)
Estimated rate ratio	*1.98 [0.95; 4.12]*	
Level 3	0 (0)	0.65 (0.4)
Level 2 or level 3	72.79 (14.1)	27.49 (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 6 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} (%)		
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 100 PYE (percentage of patients)		
Level 2	559.86 (50.9)	560.56 (55.0)
Estimated rate ratio	*0.99 [0.73; 1.34]*	
Level 3	4.18 (1.4)	1.80 (0.7)
Estimated rate ratio	*2.19 [0.20; 24.44]*	
Level 2 or level 3	564.05 (51.5)	562.36 (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 7).

Table 7 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 100 PYE (percentage of patients)		
Level 2	1959.83 (84.8)	1025.53 (76.4)
Estimated rate ratio	*1.88 [1.53; 2.32]*	
Level 3	33.03 (3.1)	11.80 (3.1)
Estimated rate ratio	*2.08 [0.39; 10.96]*	
Level 2 or level 3	1992.86 (85.2)	1037.33 (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.

Paediatric population

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

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. The insulin receptor is activated by insulin icodec leading to an evenly distributed glucose-lowering effect across the dosing interval of one week. Due to the unique mode of protraction and action, the clinically relevant parameters are represented better by the pharmacodynamic properties than the pharmacokinetic properties of insulin icodec.

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

The affinity of insulin icodec to serum albumin corresponds to a plasma protein binding of > 99% in human plasma.

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

5.3 Preclinical safety data

From *in vitro* efficacy pharmacology studies, it is clear that insulin icodec binds specifically to the human insulin receptor and results in the same pharmacological effects as human insulin.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Metacresol
Phenol
Zinc acetate
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Substances added to Awiqli may cause degradation of insulin icodec.

Awiqli must not be added to infusion fluids.

6.3 Shelf life

30 months.

Shelf life after first opening of the pen

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

6.4 Special precautions for storage

Before first use

Store in a refrigerator (2 °C-8 °C).

Do not freeze. Keep away from the freezing element.
Keep the cap on the pen in order to protect from light.

After first opening or if carried as a spare

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

6.5 Nature and contents of container

1, 1.5 or 3 mL solution in a cartridge (Type I glass) with a plunger (halobutyl) and a laminated rubber sheet (halobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

The 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 or 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 or 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 or without 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.

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

For detailed instructions for use, see the package leaflet.

7. MARKETING AUTHORISATION HOLDER

Manufactured by:
Novo Nordisk A/S, Hillerød, Denmark

Imported by:
Nordisk Pharma (Thailand) Ltd., Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBERS

Thai reg. no

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Approval date from Thai FDA

10. DATE OF REVISION OF THE TEXT

25 April 2024

Detailed information on this medicinal product is available on the website of the Thai FDA.

Instructions for use

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

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

Always start by checking your pen label to make sure that it contains Awiqli.

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

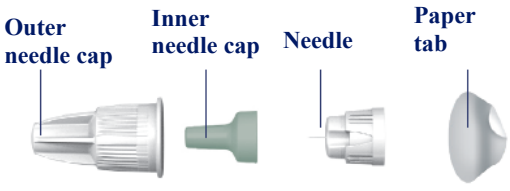
Once-weekly injection

Awiqli pen (example)

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

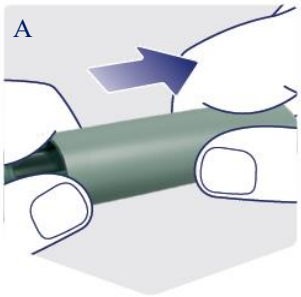
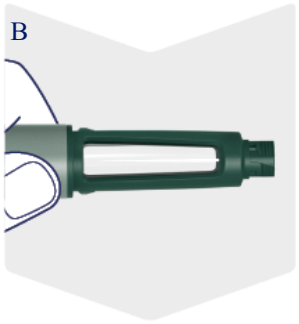
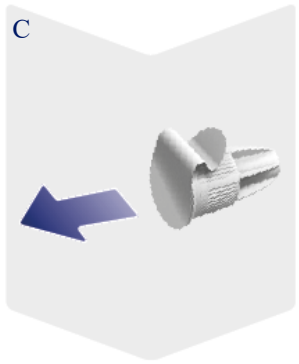
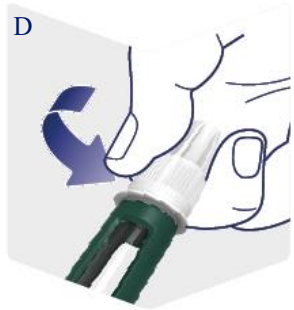
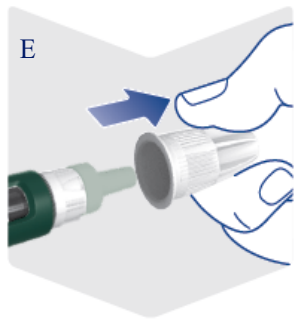
NovoFine Plus Needle (example)

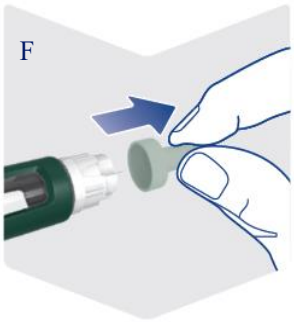
About your needles
Always use a new needle for each injection. Check the flow as described in 'Step 2' and use a new needle for each injection. Always remove the needle after each use.



Step 1 Prepare your pen with a new needle

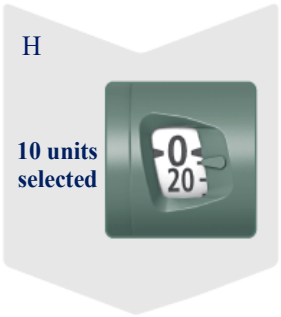
- **Check the name and concentration on the pen label** to make sure that your pen contains insulin icodec 700 units/mL.
- Pull off the pen cap. See Figure A.

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



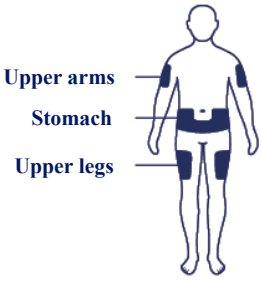
Step 2 Check the flow before each injection

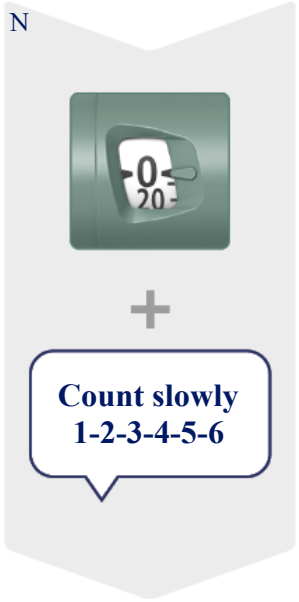
- **Always check the flow before each injection.** This helps you to ensure you will get your full Awiqli dose.
- Turn the dose selector clockwise until you see the first mark (10 units) on the dose counter. See Figure G.
- Make sure that the mark lines up with the dose pointer. See Figure H.

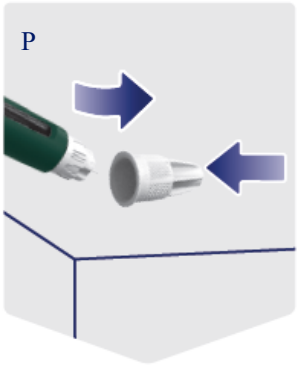
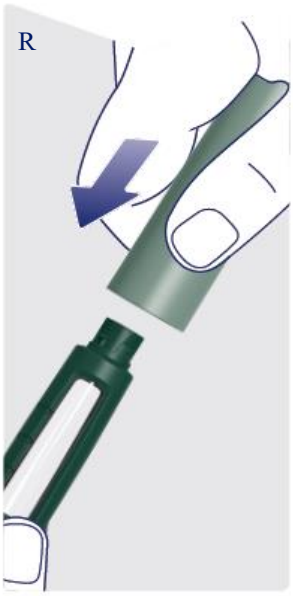


- Hold the pen with the needle pointing up.
- **Press and hold in the dose button until the dose counter shows -0-.** The -0- must line up with the dose pointer.
- A drop of Awiqli should appear at the needle tip. This drop indicates that your pen is ready for use. See Figure I.
- **If a drop does not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

	I 
Step 3 Set your dose	
• Check that the dose pointer is set at 0. See Figure J. • Turn the dose selector to select the number of units you need to inject. • **Make sure you select your intended dose.** See Figure K.	J 
• The units shown in the dose counter will guide you to your dose. The dose can be increased by 10 units at a time. • You will hear a 'click' every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear. • If you select a wrong dose, you can turn the dose selector forwards or backwards to the correct dose.	

	K 
• When your dose lines up with the dose pointer, you have selected your dose. **Make sure you select your intended dose.** • The pictures show examples of how to choose your dose correctly. See Figure L. • If the dose counter stops before you reach your prescribed dose, see the section **'Do you have enough Awiqli?'** below these instructions.	L **70 units selected**  **270 units selected** 
Choose your injection site • Choose an injection site on your stomach (keep a 5 cm distance from your belly button), upper legs, or upper arms. • You may inject in the same body area each week, but make sure it is not in the same spot that was used for your last injection.	
Step 4 Inject your dose	

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

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

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

Important information

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

Caring for your pen

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

Signature Page for VV-LAB-116651 v1.0

Approval	PPHM (Patarin Phanthumitr) Regulatory 30-Jun-2024 14:44:45 GMT+0000

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