swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Awiqli FlexTouch

International non-proprietary name: insulin icodec
Pharmaceutical form: solution for injection in prefilled pen
Dosage strength(s): 700 U/ml
Route(s) of administration: subcutaneous use
Marketing authorisation holder: Novo Nordisk Pharma AG
Marketing authorisation no.: 69389
Decision and decision date: approved on 07.03.2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the plasma concentration-time curve
BMI	Body mass index
BW	Body weight
CGM	Continuous glucose monitoring
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DKA	Diabetic ketoacidosis
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EAC	Event Adjudication Committee
EMA	European Medicines Agency
ETD	Estimated treatment difference
ETR	Estimated treatment ratio
FDA	Food and Drug Administration (USA)
FPG	Fasting plasma glucose
GIR	Glucose infusion rate
GLP	Good Laboratory Practice
GLP-1	Glucagon like peptide 1
HbA1c	Glycosylated haemoglobin
HR	Hazard ratio
IAsp	Insulin aspart
ICH	International Council for Harmonisation
Ico	Insulin icodec
IDeg	Insulin degludec
IGF-1	Insulin-like growth factor 1
IGlar	Insulin glargine
IR	Insulin receptor
LoQ	List of Questions
MACE	Major adverse cardiovascular events
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NPH insulin	Neutral protamine Hagedorn insulin
PD	Pharmacodynamics
PG	Plasma glucose concentration
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PSP	Pediatric study plan (US FDA)
PYE	Patient years exposure
QD	Once daily
QW	Once weekly
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous(ly)
SMPG	Self-measured plasma glucose
SwissPAR	Swiss Public Assessment Report

T1D	Type 1 diabetes
T2D	Type 1 diabetes
TAR	Time above glycaemic range
TBR	Time below glycaemic range
TEAE	Treatment-emergent adverse event
TIR	Time in range
T_{max}	Time taken to reach the maximum concentration
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for insulin icodec in the above-mentioned medicinal product.

Work-sharing procedure
The applicant requested a work-sharing procedure with Australia, Canada, and Singapore.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA) and Swissmedic - and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of diabetes mellitus in adults.

2.2.2 Approved indication

Treatment of diabetes mellitus in adults.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The determination of insulin dosing is based on individual needs. In people with type 2 diabetes, insulin icodec can be administered alone or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin. In people with type 1 diabetes, insulin icodec must be combined with bolus insulin to cover mealtime insulin requirements.
Insulin icodec is a basal insulin intended for once-weekly subcutaneous administration, to be taken on the same day of the week.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	14 April 2023
Formal control completed	17 May 2023
List of Questions (LoQ)	14 September 2023
Response to LoQ	12 November 2023
Preliminary decision	22 December 2023
Response to preliminary decision	17 January 2024
Labelling corrections	7 February 2024
Response to labelling corrections	21 February 2024
Final decision	7 March 2024
Decision	approval

3 Medical context

The various basal insulin analogues currently available for the treatment of type 1 diabetes (T1D) and type 2 diabetes (T2D) need to be administered at least once daily. Novel ultralong-acting insulin analogues (e.g., with a weekly dosing interval) can reduce the number of injections, potentially improving patient convenience and compliance. Insulin icodec (Ico) is a novel insulin analogue possessing an exceptionally long plasma half-life, which suits the drug for once-weekly subcutaneous administration.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

5 Nonclinical aspects

The applicant's focus of the nonclinical testing was to demonstrate the desired long pharmacokinetic (PK) and pharmacodynamic (PD) effects of insulin icodec (long-acting insulin analogue) while maintaining the same biological and safety profile as human insulin. Human insulin was included as comparator in most pharmacology studies and in the 52-week rat toxicity study, which included a carcinogenicity assessment. Relevant ICH guidelines and the EMA "Points to Consider Document on the Non-Clinical Assessment of the Carcinogenic Potential of Insulin Analogues" (CPMP/SWP/372/01) were considered for the nonclinical safety programme.

5.1 Pharmacology

Insulin icodec showed *in vitro* a low binding affinity towards the human insulin receptor (IR; binding affinity relative to human insulin <1%) and towards IR-A and IR-B isoforms from animal species (rat, pig, dog). Furthermore, insulin icodec demonstrated *in vitro* a low binding affinity towards the insulin-like growth factor 1 (IGF-1) receptor from human, rat and dog.
Insulin icodec stimulated *in vitro* the same biological responses (IR activation, metabolic and mitogenic responses) as native human insulin, albeit with lower potency, which is consistent with the lower receptor affinity. The balance of metabolic:mitogenic potency is considered to be comparable with native human insulin. Presence of human serum albumin reduced the binding affinity and *in vitro* potency of insulin icodec, in line with the albumin-binding properties of the compound.
Nonclinical *in vivo* pharmacology studies with insulin icodec were conducted in diabetic rats and normoglycaemic dogs and pigs. In Zucker Diabetic Fatty rats, insulin icodec lowered HbA1c levels in a dose-dependent manner, with an estimated potency of 40-50% compared to neutral protamine Hagedorn (NPH) insulin. The glucodynamic potency of insulin icodec was assessed by the hyperinsulinaemic euglycaemic clamp technique in dogs and pigs. Insulin icodec showed an about 2-fold higher potency relative to an authorised long-acting insulin analogue in these studies.
Based on the results of studies on secondary pharmacodynamics and the observations in the repeated-dose toxicity studies, the off-target interaction potential of insulin icodec is considered low.
The *in vitro* and *in vivo* safety pharmacology studies did not reveal a risk for effects on the cardiovascular, central nervous, or respiratory systems. It is to note that the maximum doses used in the animal studies were associated with plasma C_{max} values that were slightly above (rat, 2.5-fold) or below (dog) the average clinical C_{max}. Higher doses were not tested due to the risk of hypoglycaemia.

5.2 Pharmacokinetics

The PK of insulin icodec following single and repeated subcutaneous (SC) administration was characterised in the animal species that were used for safety assessment (rat, dog, and rabbit). In addition, several studies in pigs were conducted to investigate the influence of different zinc concentrations in the formulation on the PK parameters. All species exhibited linear PK with dose-proportional systemic exposure (C_{max} and AUC). There were no sex-related differences in exposure.
Based on an interspecies comparison of PK parameters normalised to a 1 nmol/kg dose, the PK of insulin icodec in animals is similar to that in humans, except that the terminal half-life in humans (173 h) is longer than in the animal species (25-28 h in rats and rabbits, 45 h in pigs, and 61 h in dogs).
Insulin icodec led to the formation of ADAs in rats and dogs. In the 8-week studies, most animals were ADA-positive, whereas the ADA incidence was low in the 26-week studies. Based on the evaluation of the PD response (effect on plasma glucose levels), a neutralising effect of the ADAs could not be excluded for some dogs in the 26-week study. However, the validity of the study was not affected as the majority of animals showed reduced blood glucose levels.
Most studies on the distribution, metabolism, and excretion of insulin icodec were conducted using tritium (^{3}H)-labelled compound. The radiolabel was either in the fatty acid ("[^{3}H]-Eic") or in the linker ("[^{3}H]-ADO") moiety.
Following single SC administration of 75 nmol/kg [^{3}H]-Eic-insulin icodec to albino rats, there was wide distribution of radioactivity, except from the eye lens, with tissue T_{max} generally at 12-24 h post dose.

Tissues with highest observed exposure levels were tooth pulp, kidney cortex, bile duct compartment, and blood. Lowest exposure levels were seen in brain and spinal cord.
In rat and dog, blood-plasma radioactivity concentration ratios were <1, which indicates little or no association of insulin icodec and metabolites with red blood cells.
Insulin icodec showed *in vitro* high (>99%) binding to plasma proteins in all tested species (mouse, rat, rabbit, dog, and human) and to human serum albumin.
Based on the results of *in vitro* and *in vivo* studies, the metabolism of insulin icodec in rats and dogs is qualitatively and quantitatively similar to the metabolism in humans. The main plasma metabolites identified in animals and humans were products from disulphide bond reduction and proteolytic cleavage.
Both urine and bile/faeces were involved in the excretion of insulin icodec-related material in rats and dogs.
Pharmacokinetic drug interaction studies included an *in vitro* study to investigate a possible interaction of insulin icodec with palmitate for the binding to serum albumin. Based on the results, a clinically relevant interaction is unlikely. The effect of insulin icodec treatment on CYP450 enzyme levels was studied in liver samples from the rat 26-week toxicity study. There was a minor increase (≤2.2-fold) in the activities of several CYP450 enzymes.

5.3 Toxicology

The toxicological programme for insulin icodec consisted of repeated-dose toxicity studies in rats and dogs, limited genotoxicity testing, reproductive toxicity studies in rats and rabbits, and local tolerance studies in rabbits, LYD pigs, and Göttingen minipigs. Rat and dog were selected for safety assessment as they are both pharmacologically relevant, and these species had previously been used for the evaluation of other insulin analogues. The route of administration was SC, which is the intended clinical route of administration. Dosing frequency in repeated-dose and reproductive toxicity studies was daily in rats and rabbits and twice weekly in dogs, i.e., more often than the proposed once-weekly administration in the clinic. This is appropriate considering the shorter plasma half-lives of insulin icodec in the animal species compared to humans.
The pivotal repeated-dose toxicity studies with insulin icodec included 8- and 26-week studies in rats and dogs with 6 or 12 weeks of recovery, as well as a 52-week study in rats with carcinogenicity assessment. In the 52-week study, an additional group was treated daily with 40 nmol/kg/day NPH insulin as comparator. No study was conducted to compare insulin icodec with an authorised long-acting insulin analogue.
Dose-related decreases in blood glucose levels were seen in both species, with maximum effect at 2-8 h in rats and 12-18 h in dogs. In rats, consistently decreased plasma glucose levels were observed with repeated dosing at ≥40 nmol/kg/day in males and ≥20 nmol/kg/day in females. Following the last treatment, glucose levels reversed to control levels or were higher than control levels.
Hypoglycaemia was dose-limiting in rats and dogs. In dogs, hypoglycaemia occurred at ≥18 nmol/kg; therefore, the high dose level was reduced in the 26-week study to 12 nmol/kg twice weekly, which was associated with an exposure below (0.6-fold) the average clinical exposure. In rats, hypoglycaemia-related clinical signs and mortalities were observed at ≥40 nmol/kg/day in females and ≥60 nmol/kg/day in males, associated with an exposure 2.0-fold (females) or 3.7-fold (males) the average clinical exposure. In the 52-week study, signs of hypoglycaemia and related mortalities occurred more frequently in animals treated with 40 nmol/kg/day NPH insulin than with the same dose level of insulin icodec. This is consistent with the blood or plasma glucose data obtained after dosing: NPH insulin induced marked decreases, whereas the effect in animals treated with insulin icodec was less pronounced. Hypoglycaemia is an identified risk of insulin icodec treatment; this is addressed in the information for healthcare professionals.
Except for hypoglycaemia, insulin icodec-related findings in dogs were rather minor, e.g., increased appetite and body weight gain or decreased liver weight, and there were no histopathological changes.
In rats, additional findings with insulin icodec treatment included increased body weight gain and food consumption, changes in clinical chemistry parameters, decreased liver weights, and several

microscopic findings (mainly in pancreas, liver, sciatic or tibial nerve, skeletal muscle, and brown fat). All effects were attributed to the blood glucose-lowering effect of insulin icodec. Therefore, the relevance of these effects in the normoglycaemic animals for patients with diabetes mellitus is considered low. It was noted that the incidence of effects on peripheral nervous system (axonal degeneration in sciatic and/or tibial nerve) and muscle (myofibre degeneration) in rats treated with insulin icodec in the 52-week study was higher compared to the group treated with NPH insulin. Thus, the long duration, rather than the severity of the pharmacological effect on blood glucose levels, appears to be more relevant for the induction of peripheral neuropathy and secondary effects in muscles in rats.
Insulin icodec tested negative for mutagenicity in a non-GLP bacterial assay. Based on (Q)SAR analysis, the linker+fatty acid moiety has no genotoxic potential.
Standard carcinogenicity studies with insulin icodec were not conducted with reference to ICH S6. Due to the known growth-promoting properties of insulin, the mitogenic/tumour-promoting potential was investigated *in vitro* and *in vivo* based on the EMA “Points to Consider” document. Insulin icodec showed *in vitro* low affinity towards the IR and the IGF-1 receptor and low mitogenic activity (≤2% relative to normal human insulin) in various cell lines, including the mammary tumour cell line MCF-7. IGF-1 and Insulin X-10 were used as positive controls in these assays and had a significantly higher mitogenic potential than human insulin. The 52-week repeated-dose study in Sprague Dawley rats included palpation for tissue masses and evaluation of (pre-)neoplastic lesions, with a focus on the mammary gland. No carcinogenic effects of the treatment with insulin icodec or NPH insulin were observed in this study. The incidence of tumours and the incidence/severity of hyperplastic findings in the mammary gland were similar in the groups treated with vehicle, insulin icodec or NPH insulin. Based on the results of these studies, the mitogenic potential of insulin icodec does not exceed that of normal human insulin.
Insulin icodec had no effect on fertility or embryofetal development in rats. Abortions and increased pre- and post-implantation loss, but no treatment-related malformations, occurred in rabbits at ≥18 nmol/kg/day, a dose level that was associated with maternal toxicity/hypoglycaemia (exposure 1.7-fold the average clinical exposure). In the pre- and post-natal development study in rats, maternal toxicity and adverse effects on pups (clinical signs, increased mortality, decreased weight gain) were observed at 50 nmol/kg/day during Days 7-18 of lactation. No insulin icodec-related effects on F1 animals were observed at the post-weaning assessments. The plasma exposure of the maternal animals at the NOAEL for maternal toxicity and pre-/post-natal survival (35 nmol/kg/day) was below (0.9-fold) the average clinical exposure. The applicant considered the adverse findings in the F1 pups at the 50 nmol/kg/day dose as an indirect effect of insulin icodec treatment, i.e., related to the blood-glucose-lowering effect in the dams rather than elicited by exposure via milk. This statement is supported by the data on plasma exposure in pups on Day 11 of lactation; insulin icodec levels were very low compared to the exposure of dams. Although milk transfer of insulin icodec has not been studied, the presence of insulin icodec in plasma from rat pups during the later phase of lactation indicates uptake from the milk rather than by *in utero* exposure. Thus, insulin icodec should not be used during breastfeeding.
In the local tolerance studies, mild inflammatory reactions were observed at the SC and intravenous injection sites. In the 13-week repeated-dose SC study in Göttingen minipigs with weekly administration of the formulation proposed for marketing, erythema (grade 1) and swelling (mostly grade 1-2) were more frequently observed with the insulin icodec formulation compared to placebo. Local reactions were also examined in the clinical trials, and the findings are similar to those in the nonclinical studies.
The specified impurities in insulin icodec drug product were qualified by the toxicity studies. The applicant also prepared an adequate assessment of impurities according to ICH M7. There are no concerns with regard to the excipients.
Insulin icodec is unlikely to cause a significant risk to the environment.

5.4 Nonclinical conclusions

Overall, the pharmacology and toxicological profile of insulin icodec were adequately characterised in the nonclinical studies. The effects observed in the toxicity studies were related to exaggerated pharmacology and are therefore considered of low relevance for patients with diabetes mellitus. Based on the results of *in vitro* and *in vivo* studies, the mitogenic potential of insulin icodec does not exceed that of normal human insulin. From the preclinical standpoint, the application is approvable.

6 Clinical aspects

6.1 Clinical pharmacology

The pharmacokinetic (PK) and pharmacodynamic (PD) properties in T1D and T2D patients were evaluated in nine Phase 1 studies. Sparse PK samples were collected in one Phase 2 study and four Phase 3 studies and contributed exclusively to the population PK analysis. In the majority of Phase 1 studies, insulin icodec was administered as individual doses based on run-in periods. If a comparator was included in the study, QD insulin glargine (IGlar) or insulin degludec (IDec) were administered.

Biopharmaceutical Development
Insulin icodec 700 U/ml is a solution for injection that is supplied as three variants: 3 ml volume (2100 U), 1.5 ml volume (1050 U), 1 ml volume (700 U). The final to-be-marketed drug product is a drug-device combination product containing either the 3 ml cartridge (2100 U) or 1.5 ml cartridge (1050 U and 700 U) that is assembled in product-specific PDS290 icodec pen-injectors. All clinical studies were conducted with the to-be-marketed 700 U/mL formulation.

Following the SC administration of a single insulin icodec dose in the thigh, abdomen, and upper arm, the total exposure (AUC) was overall comparable across injections sites. In contrast, the C_{max} increased by 17% and 24% when injected in the abdomen and upper arm, respectively, as compared to the thigh. Whereas the half-lives were comparable, T_{max} was longer following the administration in the thigh. As predicted by PK modelling, the C_{max} differences were smaller at steady state. In view of a similar partial glucose-lowering effect as measured by the glucose infusion rate (GIR) obtained from 36-60 h after dosing, these differences were not considered relevant.

ADME
Absorption
In Caucasian T2D patients, the median time to maximum steady state insulin icodec concentrations was 15 h to 16 h. In Caucasian T1D patients, the median time to maximum insulin icodec concentrations at steady state was 18 h.

Steady state was reached after 3 to 4 doses, and the accumulation ratio was approximately 2. Overall, insulin icodec exposure was well distributed across the dosing interval. In general, insulin icodec exposures increased with the dose.

Within-subject variability was generally low (<10%).

Distribution, metabolism, and elimination
The extension of the half-life of insulin icodec was achieved due to strong but reversible binding to albumin. As expected, plasma protein binding of insulin icodec was high (>99%), and albumin was the major binding protein. Based on the population analysis, the V/F was estimated at 9.79 L, reflecting the high protein binding.

The predominant circulating entity was insulin icodec. The identified metabolites do not exert any pharmacological activity. No unique insulin icodec metabolites were found in vitro. Insulin icodec was primarily eliminated via insulin receptor binding, and non-specific degradation was minor. Only a small proportion of subjects with different degrees of renal impairment had detectable insulin icodec in urine.

The mean half-lives in T2D and T1D patients were 155 h to 196 h and 175 h, respectively.

Special populations
The impact of kidney function on the PK of insulin icodec following a single dose of 1.5 U/kg was investigated in a dedicated study in non-diabetic subjects with normal renal function and with mild to severe renal impairment as well as ESRD. Whereas Cmax remained approximately constant,

increasing renal impairment was associated with increased insulin icodec total exposures. AUC0-840 was increased by 16% to 21% in subjects with moderate and severe renal impairment. In a sensitivity analysis, total exposure in subjects with severe renal impairment was 26% higher when the subject with low exposure was excluded. AUC0-840 was increased by 12% to 13% in subjects with mild renal impairment and with ESRD. Generally, the half-life was prolonged in subjects with renal impairment.
The impact of liver function on the PK of insulin icodec following a single dose of 1.5 U/kg was investigated in a dedicated study in non-diabetic subjects with normal hepatic function and with mild to severe hepatic impairment. Total exposure was unchanged in subjects with mild and moderate hepatic impairment, but was increased by 13% to 15% in subjects with moderate and severe hepatic impairment. Cmax was similar in subjects with moderate/severe hepatic impairment and was 13% higher in subjects with mild hepatic impairment. Whereas T_{max} was slightly shorter in subjects with mild hepatic impairment, the half-life was prolonged in subjects with severe hepatic impairment.
No association between baseline albumin and insulin icodec exposure was observed in subjects from different renal and hepatic function groups.
Overall, the observed differences are not considered clinically relevant, and no dose adjustments are required in view of the individual titration of insulin icodec.

The concentration-time profiles in Japanese T1D and Chinese T2D patients were well distributed over the dosing interval and were comparable with those for Caucasian T1D and T2D patients, respectively. Whereas the dose-normalised exposure was slightly higher in Caucasian T1D and T2D patients, T_{max} and the half-life were similar. Of note, the mean dose was generally lower in Japanese T1D and Chinese T2D patients.

Using data from one Phase 2 and four Phase 3 studies, a population PK analysis was conducted to identify factors that account for variability of the insulin icodec PK. A total of 1244 subjects with 6939 samples were included in the population PK analysis. The PK of insulin icodec was well described by a 1-compartment model with first-order absorption and elimination. All investigated covariates were included in the full model to assess their impact. Body weight showed the biggest impact on insulin icodec PK and was characterised by decreasing exposure with increasing body weight. When adjusting for body weight, none of the investigated covariates, including age, ethnicity, race, sex, antibody level, albumin, and population were found to have a relevant effect on insulin icodec PK. Of note, the impact of hepatic and renal impairment was not evaluated. Overall, no dose adjustments are required in view of the individual titration of insulin icodec.

Interactions
Although no formal drug-drug interaction studies were conducted, interactions of insulin icodec with CYPs are unlikely. In view of the high concentration of serum albumin, the potential of insulin icodec to competitively displace albumin-bound drugs is considered highly unlikely. It has been shown in vitro that palmitic acid had no impact on the albumin binding of insulin icodec at clinically relevant concentrations.

Pharmacodynamics
Insulin icodec is a long-acting human insulin analogue covering the basal insulin requirements. Through binding to the human insulin receptor, it exerts the same pharmacological effect, i.e. glycaemic control, as human insulin. The extension of the half-life of peptides was achieved by the addition of a fatty acid side chain and the modification of the peptide backbone.

The glucose-lowering effect in T1D and T2D patients at steady state has been investigated in the Phase 1 studies using euglycaemic clamps and glucose infusion rate (GIR) as a measurement of glucose metabolism. Since the dosing interval could not be fully covered with the clamp, the PD effect during the entire week was evaluated using PK/PD modelling based on clamp measurement at the beginning and end of the interval.
In Caucasian T2D patients, the entire dosing interval was covered by the duration of the glucose-lowering effect. Furthermore, the glucose-lowering effect was close to evenly distributed.

In Caucasian T1D patients, the dosing interval was also covered by the duration of the glucose-lowering effect. In contrast to patients with T2D, the GIR effect was not evenly distributed and decreased over time. Furthermore, more fluctuations of the blood glucose levels were observed at the end of the dosing interval.
In Japanese T1D patients, similar GIR profiles as in Caucasian T1D patients were observed.

Three Phase 1 studies included insulin degludec IDeg) or insulin glargine (IGlar) as a comparator arm. In order to demonstrate a comparable PD effect, the relative bio-efficacy using AUC_{GIR} of insulin icodec and the respective comparator was determined. Based on an estimated relative bio-efficacy between 101% and 119%, it can be concluded that insulin icodec, insulin degludec, and insulin glargine have an equipotent glucose-lowering effect.

Secondary Pharmacology (Safety)
Hypoglycaemia frequency and the physiological response following double or triple doses of insulin icodec or insulin glargine in subjects with T2D were investigated. The double and the triple dose of insulin icodec and insulin glargine induced clinically significant hypoglycaemia (plasma glucose (PG) PG_{nadir} <3.0 mmol/L [<54 mg/dL]), which was the primary endpoint. Comparable proportions of patients experienced clinically significant hypoglycaemia following both double (39.5% vs. 35.7%) and triple (52.6% vs. 70.0%) doses of insulin icodec versus insulin glargine. The proportion of patients with PG_{nadir} ≤2.5 mmol/L (≤45 mg/dL) was significantly higher for insulin glargine after a triple dose. Time to recover from PG_{nadir} to PG 5.5 mol/L was comparable for insulin icodec and insulin glargine.

6.2 Dose finding and dose recommendation

Dosing of insulin varies widely depending on patients' insulin sensitivity and body weight. In order to accommodate the large differences in insulin requirements, the dose of basal insulin is generally titrated according to specific treat-to-target algorithms. Three Phase 2 studies (4383, 4465, and 4466) investigated treat-to-target titration algorithms for once weekly insulin icodec (Ico QW) in patients with T2D. Study 4383, a 26-week, randomised, double-blind, active-controlled trial in insulin-naïve patients with T2D, showed that Ico QW can provide glycaemic control comparable with that achieved with once daily insulin glargine U100 (IGlar QD) (estimated treatment difference [ETD] in HbA_{1c} [95% CI]: -0.18% [-0.38, 0.02]). The 23-week open-label (Ico QW vs. IGlar QD) study 4465 explored three titration algorithms for Ico QW, where pre-breakfast self-measured plasma glucose (SMPG) <4.4 mmol/L (80 mg/dL) and < 3.9 mmol/L (70 mg/dL), respectively, triggered dose reductions. The data from this study favoured a pre-breakfast SMPG <4.4 mmol/L (80 mg/dL). The time in range (%) for the most favourable titration algorithm B was even superior to that of the IGlar QD arm (ETD [95% CI]: 7.08% [2.12; 12.04]; p =0.0051) without a meaningful increase in the risk for hypoglycaemia (ETD [95% CI] of the time spent <3.9 mmol/L: 0.68% [-0.15, 1.50]). Study 4466 examined switching from IGlar QD with or without an initial loading dose. The loading dose provided a minor advantage regarding the time needed to restore the original level of glycaemic control, but at the cost of an increased hypoglycaemia risk.
Ultimately, a treat-to-target strategy following the dose titration algorithm illustrated below was chosen for the Phase 3 trials. Three pivotal trials (ONWARDS 2, 4, and 6) used a single loading dose for the switch from prior basal insulin to Ico QW (i.e., patients routinely received a dose Ico QW 7-fold the total daily dose of their prior basal insulin + 50% of total daily dose of their prior basal insulin).

Pre-breakfast SMPG			Dose adjustment
Value to use	mmol/L	mg/dL	U
Lowest of the SMPG values	<4.4	<80	–20
Mean of the SMPG values	4.4–7.2	80–130	0
	>7.2	>130	+20

6.3 Efficacy

Efficacy is supported by the ONWARDS programme, which consisted of six pivotal Phase 3 studies sharing most features of design and conduct. Differences between the individual trials relate to their study populations (T2D, T1D, insulin-naïve, previously treated with insulin), the active comparator, the treatment setting (e.g., clinical practice setting in the ONWARDS 5 trial), and open-label versus double blind design.[1]

	T2D: Insulin-naive			T2D: Previously insulin-treated		T1D
	ONWARDS 1	ONWARDS 3	ONWARDS 5	ONWARDS 2	ONWARDS 4	ONWARDS 6
Key trial details						
Trial design	Randomized open label	Randomized double-blind	Randomized open label real-world elements	Randomized open label	Randomized open label	Randomized open label
Estimated sample size required, N	970	580	1096	520	580	580
Study start date	November 2020	March 2021	March 2021	March 2021	May 2021	April 2021
Trial duration	78 wk (52-wk main phase +26-wk extension phase) + 5-wk follow-up period	26 wk + 5-wk follow-up period	52 wk + 5-wk follow-up period	26 wk + 5-wk follow-up period	26 wk + 5-wk follow-up period	52 wk (26-wk main phase + 26-wk extension phase) + 5-wk follow-up period
Interventions						
Icodec arm	Once-weekly icodec + non-insulin glucose-lowering agents	Once-weekly icodec + non-insulin glucose-lowering agents + once-daily placebo	Once-weekly icodec (with digital titration solution) ± non-insulin glucose-lowering agents	Once-weekly icodec ± non-insulin glucose-lowering agents	Once-weekly icodec ± non-insulin glucose-lowering agents + aspart 2-4 times daily	Once-weekly icodec + aspart ≥2 times daily
Comparator arm	Once-daily glargine U100 + non-insulin glucose-lowering agents	Once-daily degludec + non-insulin glucose-lowering agents + once-weekly placebo	Once-daily basal insulin analogues (degludec, glargine U100 or U300) + non-insulin glucose-lowering agents	Once-daily degludec ± non-insulin glucose-lowering agents	Once-daily glargine U100 ± non-insulin glucose-lowering agents + aspart 2–4 times daily	Once-daily degludec + aspart ≥2 times daily
Key inclusion criteria						
Diagnosis	T2D diagnosed ≥180 d prior to screening					T1D diagnosed ≥1 y prior to screening
Demographics	Male or female age ≥ 18 y at the time of signing informed consent					
Screening HbA_{1c}	7.0%-11% (53.0-96.7 mmol/mol)		>7.0% (53 mmol/mol)	7.0%-10.0% (53.0-85.8 mmol/mol)		<10% (85.8 mmol/mol)
BMI, kg/m^2	≤40.0		N/A	≤40.0		N/A
Prior insulin treatment	Insulin-naive Short-term insulin treatment periods for a maximum of 14 d prior to the day of screening or prior insulin treatment for gestational diabetes are permitted			Insulin treatment ≥90 d prior to the day of screening Once-daily or twice-daily basal insulin: NPH insulin, degludec, detemir, glargine U100 or U300	Insulin treatment ≥90 d prior to the day of screening Daily basal insulin: NPH insulin, degludec, detemir, glargine U100 or U300 Bolus insulin analogue: aspart, faster aspart, lispro, faster lispro or glulisine 2-4 times daily	MDI ≥1 y prior to the day of screening
Prior non-insulin treatment	Stable doses of glucose-lowering agents ≥90 d prior to screening are permitted[g]			Stable doses of glucose-lowering agents ≥90 d prior to screening are permitted[h]		N/A

To exclude patients with prominent insulin resistance, the ONWARDS trials partially used a criterion of BMI >40 kg/m^2. All ONWARDS trials tested the primary hypothesis that Ico QW is non-inferior to its active comparator in the **change in HbA_{1c} from baseline** (primary endpoint with pre-specified non-inferiority margin of 0.3 %).

The completion rates in the pivotal trials were ~90% (ONWARDS 5) to ~97% (ONWARDS 1, 2). The patient-introduced bias for the primary (non-inferiority) hypotheses due to open label design can be considered negligible as there was no relevant imbalance in drop-outs between the treatment groups in any of the ONWARDS trials.

Tipping point analyses were performed in order to support the robustness of the results of the primary analyses. A testing hierarchy was predefined to control for type 1 error in the ONWARDS trials testing multiple confirmatory hypotheses.

The following table briefly captures relevant demographics and baseline characteristics of the study population in the ONWARDS trials in patients with T2D.

[1] Philis-Tsimikas, A., et al., *Rationale and design of the phase 3a development programme (ONWARDS 1-6 trials) investigating once-weekly insulin icodec in diabetes.* Diabetes Obes Metab, 2023. **25**(2): p. 331-341.

Study	Mean age [y]	Duration of diabetes [y]	Body weight [kg]	HbA_{1c} [%]	FPG [mg/dL]	eGFR [ml/min/1.73 m^2]
ONWARDS 1	~59	~11.5	~85	~8.5	~185	~85
ONWARDS 2 $	~62.5	nearly 17	81.5 – 83.7	~8.1	~150	~80
ONWARDS 3 $$	~58	~11	83.4 – 85.8	~8.5	176 - 187	>90
ONWARDS 4 $$$	~63	16 - 18	83.1 – 85.5	~8.3	167 - 173	~82
ONWARDS 5 $$$$	~59	~12	~93	~8.9	-	~88

$ Most common basal insulins were IGlar U100 QD, IDeg QD, and IGlar U300 QD.

$$ Most common background medications were metformin (~90%), sulphonylurea (~44%), DPP4 inhibitors (~26%), GLP-1 receptor-agonists (21.8% [Ico QW] vs. 16.3 [Idec QD]), and SGLT2 inhibitors (40.5% [Ico QW] vs. 32.3% [Idec QD]) with imbalances for the two latter classes.

$$$ Most common basal insulins used prior to randomisation were IGlar U100 QD (49.5% and 44.3% in the Ico QW and IGlar QD arms, respectively), IDeg QD (25.1% and 23.0% in the Ico QW and IGlar QD arms, respectively), and IGlar U300 QD (19.2% and 23.0% in the Ico QW and IGlar QD arms, respectively).

$$$$ Most common background medications were metformin (used by >90% of the participants), SGLT2 inhibitors (used by ~45%), and sulphonylurea (used by ~40%). Injectable GLP-1RAs were used by ~27% of the participants.

The following table summarises the efficacy results from trials in patients with T2D, where an asterisk indicates superiority versus active comparator for the primary endpoint.

Study	Estimated Treatment Difference [95% CI] Ico QW versus active comparator			
	HbA_{1c} (%) [95% CI]	Responder rate[2]	FPG (mg/dL)	TIR (%)[3]
ONWARDS 1	-0.19 [-0.36, -0.03] *	1.63 [1.24, 2.14]	-0.24 [-4.89, 4.41]	4.27 [1.92, 6.62]
ONWARDS 2	-0.22 [-0.37, -0.08] *	1.88 [1.26, 2.79]	-0.71 [-5.12, 6.54]	2.41 [-0.84, 5.65]
ONWARDS 3	-0.21 [-0.34, -0.08] *	1.84 [1.29, 2.64]	-0.38 [-6.05, 5.30]	n/a
ONWARDS 4	0.02 [-0.11, 0.15]	0.82 [0.58, 1.17]	-2.48 [-10.59, 5.63]	0.29 [-2.52, 3.09]
ONWARDS 5	-0.38 [-0.66, -0.09] *	1.66 [1.24, 2.21]	n/a	n/a

Across all trials, the glucose-lowering efficacy showed no clinically meaningful heterogeneity as illustrated for the subgroups by baseline HbA_{1c} and eGFR.[4]

[2] Proportion of patients achieving HbA1c < 7% represented as estimated odds ratio [95% CI]

[3] TIR = time in range 3.9-10.0 mmol/L (70-180 mg/dL) as measured using CGM during a predefined period (Week 48 – 56)

[4] Exceptions from this pattern were elderly patients (≥75 years) in ONWARDS 4 and 6. However, these subgroups consisted of only 10 vs. 11 (ONWARDS 4) and 3 vs. 3 (ONWARDS 6) subjects.

Estimated treatment difference in the change of HbA_{1c}

By baseline HbA_{1c} <8% | ≥8%

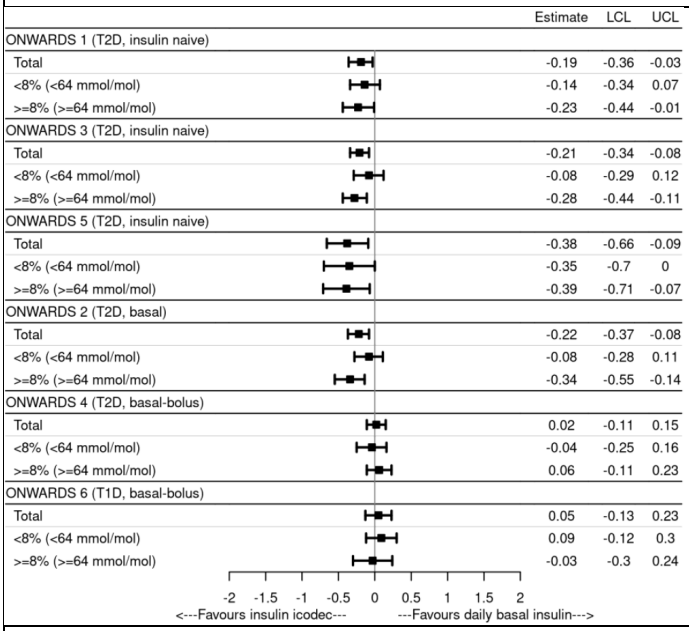


Figure 3-20 of Module 2.7.3

By baseline renal function eGFR [ml/min/1.73m²]

normal ≥90 | mildly impaired ≥60 - <90 | moderately/severely impaired <60

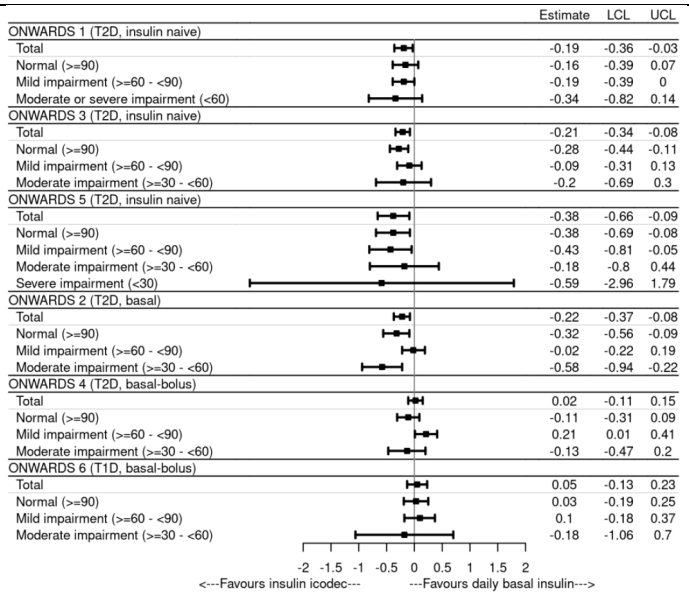


Figure 3-21 of Module 2.7.3

The findings outlined above strongly support the efficacy of Ico QW in patients with T2D. This was apparently not associated with an increased demand of weekly basal insulin. For example, the estimated treatment ratios [95% CI] were 0.96 [0.89, 1.05] and 0.92 [0.85, 0.99] in ONWARDS 1 and ONWARDS 4, respectively. Yet, across all trials, patients in the Ico QW arm gained numerically slightly more weight than patients in the active comparator arms IGlar QD arm (e.g., ETD [95% CI] in ONWARDS 4 was 0.57 kg [-0.39, 1.54]).

Finally, once-weekly administration of basal insulin appeared to have a positive impact at treatment satisfaction: the diabetes treatment satisfaction questionnaire (DTSQ) total treatment score improved significantly more in the Ico QW arm than in the active comparator arm of the ONWARDS 2 trial (ETD [95% CI]: 1.25 [0.41, 2.10]; p<0.005) and the ONWARDS 5 trial (ETD [95% CI]: 0.78 [0.10, 1.47]; p=0.0247).

ONWARDS 6 was a Phase 3 study in patients with **T1D** who were, for at least one year, on a multiple daily injection insulin therapy (as summarised below) and had an HbA_{1c} <10% (85.8 mmol/mol). All study participants per protocol used exclusively insulin aspart (IAsp) as bolus insulin. The study included a 26-week main treatment period followed by a 26-week extension phase. Subjects were randomised (1:1) to basal insulin Ico QW or IDeg QD using stratification by pre-trial basal insulin regimen (BID | QD | IGlar U300) and HbA1c (<8% | ≥8%).

Continuous glucose monitoring (CGM) was performed over the entire duration of the trial and will continue until the end of the follow-up period. Study participants had a long-standing history of T1D with a mean duration of ~20 years (i.e., they were experienced with insulin therapy).

Primary efficacy endpoint was the change in HbA_{1c} from baseline to Week 26 (**ΔA1C**). Non-confirmatory secondary endpoints were the change in fasting plasma glucose (FPG) from baseline to Week 26 (ΔFPG), the time in range 3.9-10.0 mmol/L (70-180 mg/dL) from baseline to Week 22 to Week 26 (TIR), and the change in DTSQ score for total treatment satisfaction (ΔDTSQ).

In general, demographics and baseline characteristics were well balanced between treatments. There were some imbalances with regard to the representation of the regions Asia (16.6% vs. 23.3%) and North America (36.6% vs. 29.1%). The mean baseline values for age, body weight, HbA1c, FPG, and

eGFR were ~44 years, ~78 kg, ~7.6%, 172.3 – 179.2 mg/dL, and ~98 ml/min/1.73 m^2. The most common basal insulin analogues prior to randomisation were IDeg QD (40.3% to 37.7%), IGlar QD U100 (27.9% to 25.7%), and IGlar QD U300 (15.5% to 19.9%).

Study	Estimated Treatment Difference [95% CI] Ico QW versus active comparator			
	HbA_{1c} (%) [95% CI]	Responder rate[5]	FPG (mg/dL)	TIR (%)[6]
ONWARDS 6	0.05 [-0.13, 0.23]	1.63 [1.24, 2.14]	18.6 [8.60, 28.60]	-2.0 [-4.4, 0.4]

Although robustness of the non-inferiority conclusion was supported by a sensitivity (tipping point) analysis, the data shown above clearly indicate that the outcomes for Ico QW in patients with T1D were less favourable than those described above for patients with T2D. By way of example, this is illustrated below by the time course for FPG.

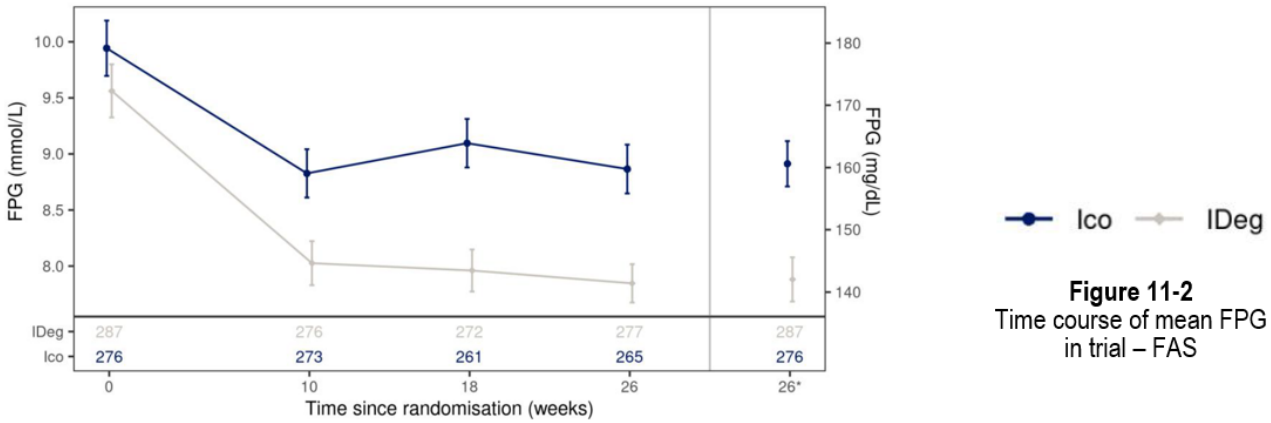


Figure 11-2
Time course of mean FPG in trial – FAS

In line with this, patients in the Ico QW treatment group spent numerically more time in hyperglycaemia[7] than patients in the IDeg QD arm (ETD [95% CI]: 1.14% [-1.34, 3.61]). Unfavourably, patients in the Ico QW treatment group at the same time spent significantly more time in hypoglycaemia[8] than patients in the IDeg QD arm (ETR [95% CI]: 1.46% [1.16, 1.85]; p=0.0012). This is ultimately reflected in the proportion of patients reaching target HbA_{1c} <7% without any level 2 or 3 hypoglycaemia, which was clearly in favour of the active comparator (9.55% [Ico QW] versus 16.74% [IDeg QD]; odds ratio [95% CI]: 0.52 [0.33, 0.85]; p=0.008).

Likewise, the improvement in DTSQ score in the Ico QW group was significantly worse than that in the IDeg QD group (ETD [95% CI]: -1.09 [-1.85, -0.34]).

The total weekly dose insulin of basal insulin was not different between treatment arms (ETR [95% CI]: 0.96 [0.9, 1.03]), and there was a negligible difference in the change in body weight (ETD [95% CI]: 0.28 kg [-0.37, 0.92]).

In conclusion, the weekly insulin Ico QW is feasible to cover the basal insulin in patients with T1D. However, the benefit-risk ratio for Ico QW in patients with T1D has to be considered much more critical than for patients with T2D given the more prominent increase in the risk of hypoglycaemia, and the less favourable outcome consistent across efficacy endpoints.

6.4 Safety

Insulin icodec is a novel basal insulin to be administered once weekly (Ico QW). Its safety profile is generally expected to match that of other insulins, particularly basal insulins.

[5] Proportion of patients achieving HbA1c < 7% represented as estimated odds ratio [95% CI]
[6] TIR = time in range 3.9-10.0 mmol/L (70-180 mg/dL) as measured using CGM during a predefined period (Week 48 – 56)
[7] Time spent > 10 mmol/l (180 mg/dL) as measured using CGM
[8] Time spent < 3 mmol/l (54 mg/dL) as measured using CGM

The safety evaluation was based on a set of clinical studies including 10 Phase 1 studies, 3 Phase 2 clinical studies, 6 global Phase 3 studies [5 in T2D and 1 in T1D]).[9]

The total exposure to insulin icodec in the on-treatment/main-on-treatment observation period was 1681.23 patient years exposure (PYE) in the Phase 3a pool, 1538.92 PYE in the T2D pool and 142.31 PYE in T1D.

This amount is considered sufficient for assessing the safety profile of Ico in the target populations, also taking into account the fact that insulin icodec uses technologies of currently marketed insulin analogues and peptide receptor-agonists analogous to the native GLP-1.

The number and proportion of subjects exposed to trial product by month were similar in the Ico QW and QD basal insulin groups in the Phase 3 pool. The decrease in exposure for ≥6 compared to ≥8 months reflects the fact that the treatment duration in ONWARDS 2-4 and main part of ONWARDS 6 was 26 weeks, while the duration was 52 weeks for ONWARDS 1 (main part) and ONWARDS 5.

Subject disposition, baseline characteristics and demography were generally well balanced across treatment groups for individual trials and pooled data.

The proportion of subjects reporting AEs was generally comparable between Ico QW and QD basal insulin groups, across the individual trials. Differences in trial duration, trial population and trial design account for the differences seen between trials.

Table 2-1 Summary of AEs reported in phase 3a trials – on-treatment/main-on-treatment – safety analysis set

Trial / duration (weeks)		Total AEs		Serious AEs		Severe AEs	
		Insulin icodec	Daily basal insulin	Insulin icodec	Daily basal insulin	Insulin icodec	Daily basal insulin
ONWARDS 1 (4477) / 52[a]	%	71.3	68.1	10.4	10.0	3.7	4.1
	R	252.53	239.57	15.23	15.05	5.35	7.01
ONWARDS 2 (4478) / 26	%	61.5	51.0	8.4	6.1	4.2	4.2
	R	300.17	214.70	19.32	13.09	10.95	8.51
ONWARDS 3 (4479) / 26	%	60.4	56.8	5.1	5.1	4.4	1.4
	R	299.01	247.76	12.87	10.52	8.19	2.34
ONWARDS 4 (4480) / 26	%	58.8	57.4	7.6	8.6	4.5	4.1
	R	271.87	329.74	20.91	19.78	11.95	8.39
ONWARDS 5 (4481) / 52	%	51.5	50.2	8.3	10.6	5.2	7.1
	R	146.37	141.78	12.33	15.16	6.08	11.24
ONWARDS 6 (4625) / 26[a]	%	65.2	65.1	3.8	2.4	3.1	1.4
	R	356.27	429.50	10.54	6.24	7.03	3.47

The lower incidence of non-serious AEs in the ONWARDS 5 trial, regardless of its 52-week duration, is likely related to the trial design, which resembles standard clinical practice with fewer site visits.

Similarly, the lower incidence of SAEs in the ONWARDS 6 trial is explained by the younger age (i.e., fewer comorbidities) of the T1DM population enrolled in this trial.

COVID-19 and nasopharyngitis were the most commonly reported AEs across all ONWARDS trials followed by diarrhoea in the T2D population (while frequency was lower in the T1D population).

Overall, the data in the Phase 3 pool were consistent with the data in the individual trials.

Similar proportions of subjects in the Ico QW and QD basal insulin groups reported AEs, SAEs, and severe AEs. Similar rates of AEs by seriousness, severity, and relationship to trial product were also observed (Figure 2-2).

[9] **Note:** The extension parts of the ONWARDS 1 and 6 trials were still ongoing at the cut-off date for the application.

Figure 2-2 Adverse events – on-treatment/main-on-treatment – overview plot – safety analysis set – phase 3a pool

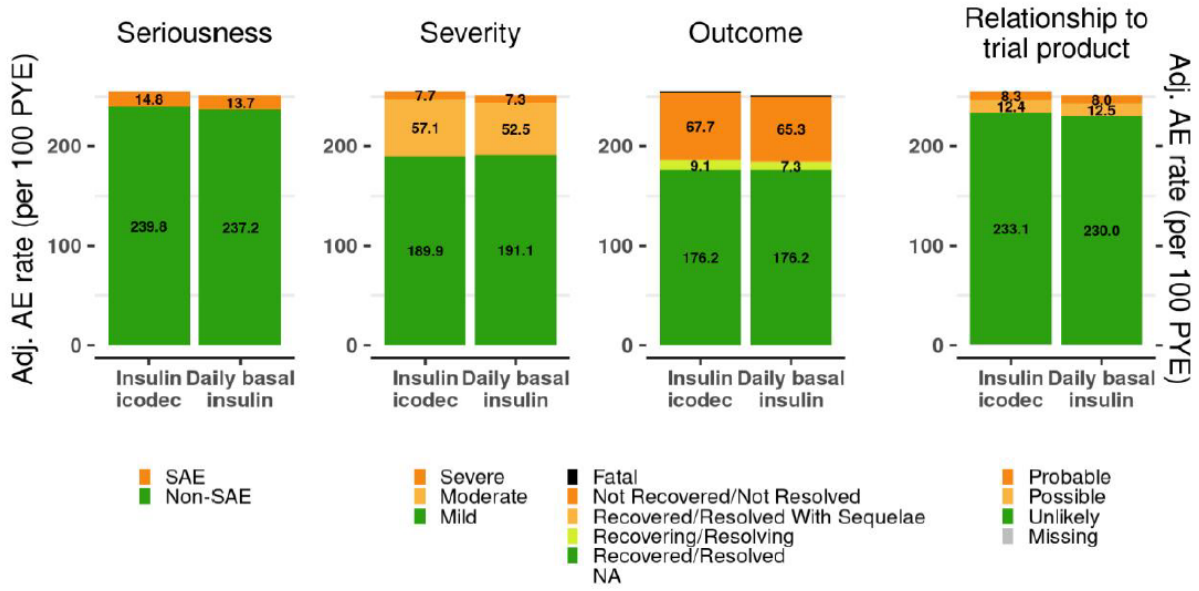


Table 2-5 Adverse events by system organ class and preferred term - most frequent [>=1%] reported in same or greater proportion of subjects on insulin icodec vs on daily basal insulin - on-treatment/main-on- treatment - summary - safety analysis set - phase 3a pool

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYE (years)	1681.23				1680.58			
Events	476	(21.9)	779	51.15	401	(18.5)	593	39.38
Infections and infestations								
Nasopharyngitis	117	(5.4)	141	10.08	115	(5.3)	135	9.65
Upper respiratory tract infection	68	(3.1)	81	4.86	52	(2.4)	56	3.54
Gastroenteritis	32	(1.5)	33	2.45	18	(0.8)	19	1.34
Bronchitis	30	(1.4)	31	2.05	19	(0.9)	19	1.20
Gastrointestinal disorders								
Diarrhoea	89	(4.1)	108	6.65	55	(2.5)	57	3.70
Nausea	41	(1.9)	42	2.58	35	(1.6)	37	2.47
Vomiting	31	(1.4)	39	2.79	21	(1.0)	24	1.55
Nervous system disorders								
Headache	70	(3.2)	92	6.52	64	(2.9)	80	5.30
Dizziness	40	(1.8)	51	3.18	39	(1.8)	47	3.07

Musculoskeletal and connective tissue disorders								
Pain in extremity	37	(1.7)	39	2.31	37	(1.7)	43	2.90
Muscle spasms	25	(1.2)	27	1.79	9	(0.4)	9	0.52
General disorders and administration site conditions								
Fatigue	32	(1.5)	36	2.31	16	(0.7)	16	0.91
Eye disorders								
Cataract	28	(1.3)	33	1.97	27	(1.2)	30	1.83
Respiratory, thoracic and mediastinal disorders								
Oropharyngeal pain	24	(1.1)	26	1.60	19	(0.9)	21	1.41

The proportions of subjects with fatal outcome were low and similar for Ico QW and QD basal insulin. A total of 27 deaths were reported across the 18 trials that included insulin icodec treatment. The 27 deaths (33 fatal AEs) occurred in 6 Phase 3 trials (14 [18 fatal AEs] in Ico QW group and 13 [15 fatal AEs] in QD basal insulin group). Of the 14 deaths in the Ico QW group, 13 occurred in the T2D population and 1 in the T1D population. All events were judged by the investigator as unlikely related to the trial product.

The proportions of subjects with SAEs and rates of SAEs in the Phase 3 pool were low and similar for Ico QW (7.7%; 14.87 events per 100 PYE) and QD basal insulin (7.8%; 13.73 events per 100 PYE).

In the T1D population (ONWARDS 6), the proportions of subjects with and rates of reported SAEs were higher in the Ico QW group (3.8%; 10.54 events per 100 PYE, respectively) compared to the insulin degludec group (2.4%; 6.24 events per 100 PYE, respectively), of which only **hypoglycaemia** was reported more than once in either treatment group.

Adverse events of special interest (AESI)

1. *HYPOGLYCAEMIA*

Hypoglycaemia is the most common adverse effect of insulin therapy and may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemic events represent a major safety concern.

The results from the ONWARDS programme clearly suggest an increased risk of hypoglycaemia in patients treated with once-weekly insulin icodec (Ico QW) as compared with patients who received the once-daily basal insulin analogues (QD basal insulin). This risk was most prominently seen in patients with T1D. The findings leading to this conclusion are consistent throughout the Phase 3 ONWARDS programme and relate to time below glycaemic range (TBR) (time spent <3.0 mmol), the rates of hypoglycaemic episodes, and their temporal relationship with time of dose administration.

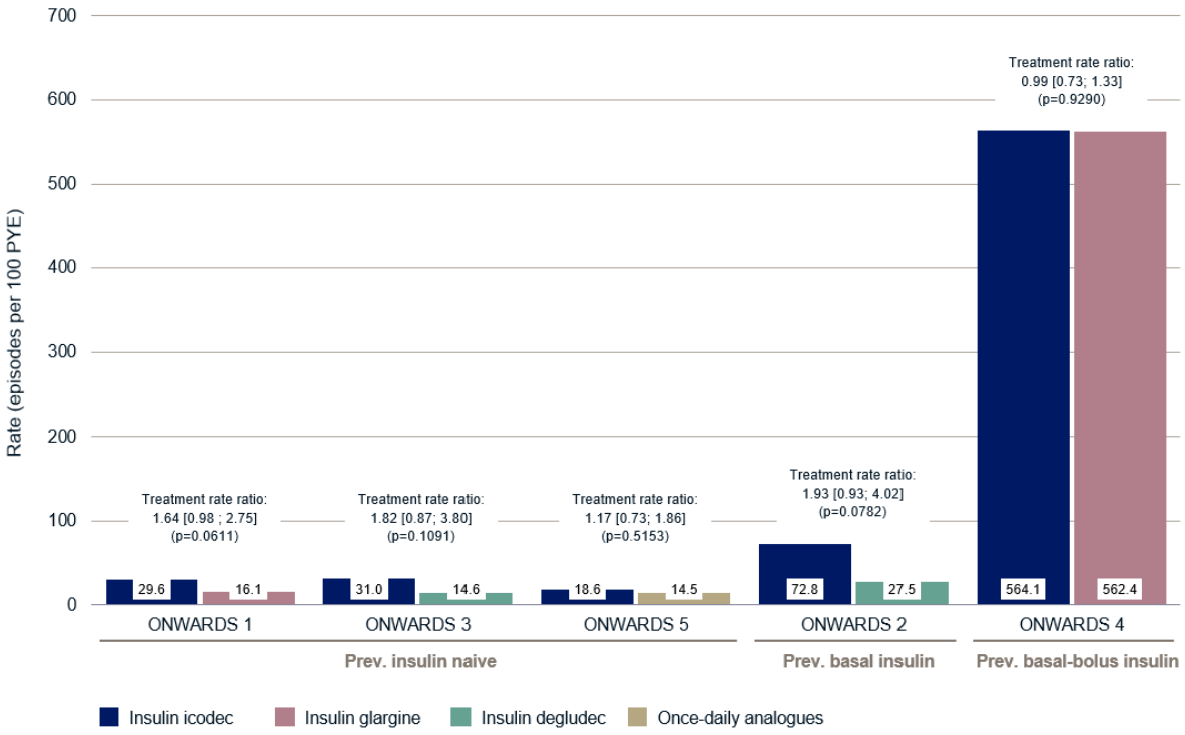
Patients with T2D

Insulin-naïve patients in the Ico QW arm of the ONWARDS 1 had numerically larger TBR than the active control group (estimated treatment ratio (ETR) [95% CI]: 1.27 [0.94, 1.71]). In parallel, patients in the Ico QW arm had an excess of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes (29.64 vs. 16.08 events per 100 PYE).

Likewise, patients switching from another basal insulin to Ico QW (ONWARDS 2) showed a numerical increase in TBR compared with the active comparator (ETR [95% CI]: 1.37 [0.92, 2.04]) which was reflected in an increased rate of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes (72.79 vs. 27.49 events per 100 PYE).

Similar observations were made for other insulin-naïve patients in ONWARDS 3 and 5, as illustrated in the figure below.

Figure 2-4 Rates of severe (level 3) or clinically significant (level 2) hypoglycaemic episodes in the T2D population - on-treatment/main-on-treatment - summary



Reassuringly, the proportion (rates) of subjects experiencing severe (level 3) hypoglycaemic episodes across all Phase 3 trials was low in both the Ico QW and the QD basal insulin groups in ONWARDS 1-5 in the different T2D populations (cf. Table 2-16).

Table 2-16 Severe (level 3) hypoglycaemic episodes in the T2D population - on-treatment/main-on-treatment - summary - safety analysis set

	Insulin icodec				Daily basal insulin			
	N	(%)	E	R	N	(%)	E	R
T2D, insulin-naïve								
ONWARDS 1								
Number of subjects	492				492			
Severe hypoglycaemia (level 3)	1	(0.2)	1	0.21	3	(0.6)	3	0.62
ONWARDS 3								
Number of subjects	293				294			
Severe hypoglycaemia (level 3)	0				2	(0.7)	2	1.17
ONWARDS 5								
Number of subjects	542				538			
Severe hypoglycaemia (level 3)	0				4	(0.7)	5	0.89
T2D, basal insulin								
ONWARDS 2								
Number of subjects	262				263			
Severe hypoglycaemia (level 3)	0				1	(0.4)	1	0.65
T2D, basal-bolus insulin								
ONWARDS 4								
Number of subjects	291				291			
Severe hypoglycaemia (level 3)	4	(1.4)	7	4.18	2	(0.7)	3	1.80

In patients who were insulin-naïve (ONWARDS 1, 3 and 5) or previously on basal insulin (ONWARDS 2), the proportion of subjects with severe (level 3) hypoglycaemic episodes and the rates were even

lower in the Ico QW groups than in the QD basal insulin groups. Across the four trials in insulin-naïve patients with T2D, only a single severe (level 3) hypoglycaemic episode was reported for Ico QW compared to a total of 11 episodes (in 10 subjects) with QD basal insulin.

Severe (level 3) hypoglycaemic episodes were numerically more frequent in the Ico QW group versus the QD basal insulin group [IGlar] (4.18 vs. 1.8 events per 100 PYE) only in patients with a more advanced stage of T2D who already used a basal-bolus regimen (ONWARDS 4). ONWARDS 4 also found a numerical increase in TBR in the Ico QW group (ETR [95% CI]: 1.20 [0.91, 1.58]). Yet, these data are somewhat difficult to interpret considering that a basal-bolus insulin regimen was used.

Patients with T1D (ONWARDS 6)

There was a statistically significant increase in TBR in patients treated with Ico QW versus the control group receiving IDeg QD (ETR [95% CI]: 1.46 [1.16, 1.85]), which was paralleled by an excess of severe (level 3) hypoglycaemic episodes (including nocturnal).

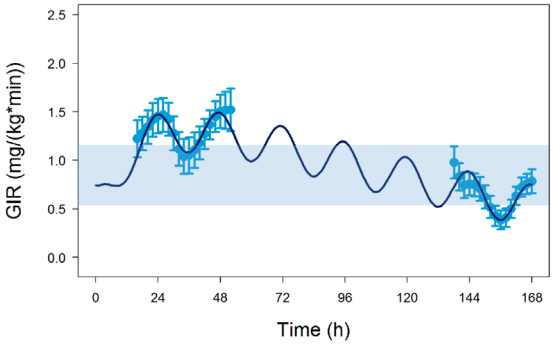
	Insulin icodec				Daily basal insulin			
	N	(%)	E	R	N	(%)	E	R
T1D, basal-bolus insulin								
ONWARDS 6								
Number of subjects	290				292			
Overall glycaemic episodes								
Severe hypoglycaemia (level 3)	9	(3.1)	47	33.03	9	(3.1)	17	11.80
Nocturnal hypoglycaemic episodes								
Severe hypoglycaemia (level 3)	2	(0.7)	5	3.51	3	(1.0)	3	2.08

Similar dramatic increases in event rates were observed for clinically significant (level 2) and alert value (level 1) hypoglycaemic episodes.

Temporal relationship of hypoglycaemic episodes with the time of dose administration

The elevated risk of hypoglycaemia described so far represents an average increase over the entire treatment period, while it is actually due to a transient overshoot inherent to the PK/PD profile of Ico QW.

The PD profile of Ico QW in patients with T1D shown below suggest a peak of hypoglycaemic events within the first 1-3 days after administration of the weekly dose.



Modified from Figure 11-11 of CSR 4225
The shaded area indicates the range accommodating the GIR excursions with QD basal insulins

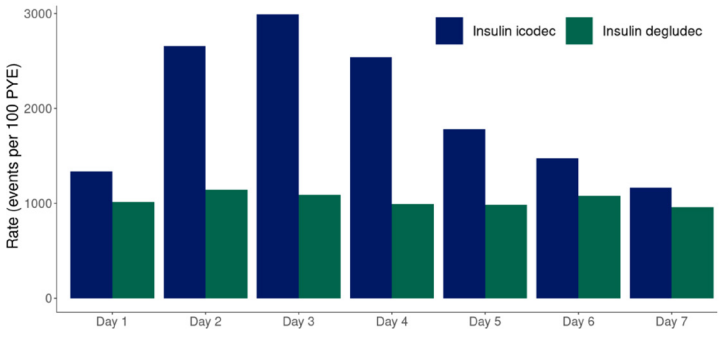
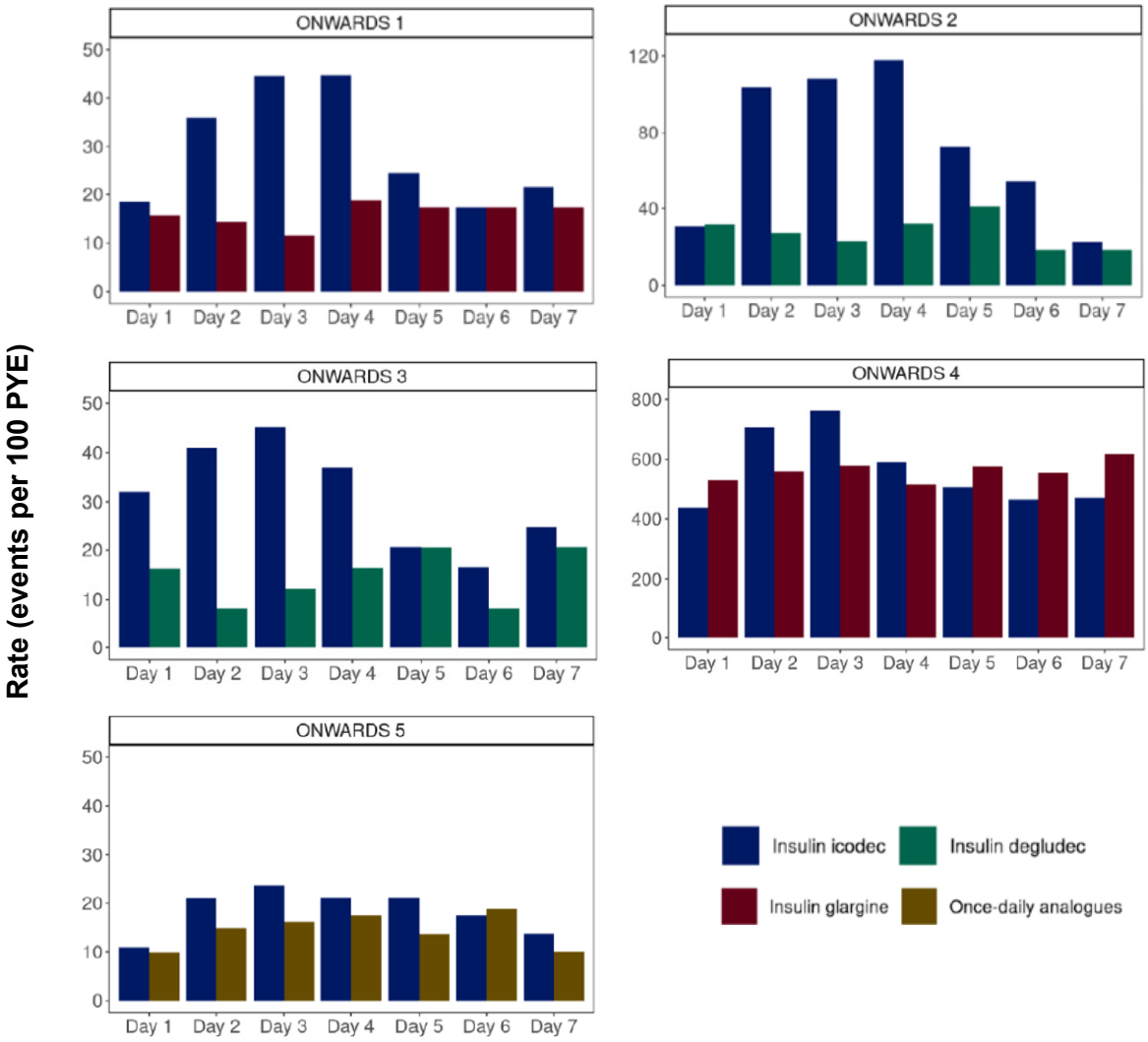


Figure 2-11 from Module 2.7.4

Indeed, the analysis of hypoglycaemia over the dosing interval of 7 days (shown on the right above) identified a marked peak of events with Ico QW versus IDeg QD between Day 2 and Day 4 which perfectly mirrored differences in their PK/PD profile.

As illustrated below, patients with T2D exhibit a similar profile of their weekly risk of hypoglycaemia.



2. *Neoplasms*

The number [rate] of neoplasm AEs was 74 in 62 subjects [4.44 events per 100 PYE] and 86 events in 66 subjects [5.18 events per 100 PYE] in the Ico QW group and the QD basal insulin group. The corresponding proportions were 2.9% and 3.0%.

Table 2-26 Neoplasms (predefined MedDRA search) – in-trial – summary – safety analysis set – phase 3a pool

	Insulin icodec				Daily basal insulin			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2170				2170			
PYO (years)	1707.11				1702.14			
Events	62	(2.9)	74	4.44	66	(3.0)	86	5.18
Serious								
Yes	17	(0.8)	20	1.16	22	(1.0)	26	1.43
No	49	(2.3)	54	3.29	50	(2.3)	60	3.75
Missing	0				0			
Related to basal insulin								
Probable	0				0			
Possible	0				0			
Unlikely	62	(2.9)	74	4.44	66	(3.0)	86	5.18
Missing	0				0			

All neoplasm AEs were judged by the investigator as unlikely related to the trial product.

In conclusion, there were no obvious imbalances between treatment groups suggesting an increased risk for neoplasms in patients treated with Ico QW. However, the database available is rather small to finally disregard this safety concern.

3. Cardiovascular disorders

The currently available data for the cardiovascular (CV) safety do not suggest an increased risk in Ico QW-treated patients. The numbers of EAC-confirmed MACE were generally small and occurred with similar incidence in the two treatment groups examined. In fact, the meta-analysis performed even suggests a numerically better outcome with Ico QW ($HR_{Ico\ QW/QD\ basal\ insulin}$ [95% CI]: 0.84 [0.48, 1.49]). In line with this, there were also no clinically relevant differences between treatment groups with regard to ECG data. One uncertainty related to the conclusion reached is the premature database.

4. Retinal disorders

The safety database available provided no hint of an increased risk of retinal disorders in the patients treated with Ico QW versus QD basal insulin.

The rate of AEs within the MedDRA search for diabetic retinopathy or maculopathy was similar in the two treatment groups (9.85 [Ico QW] versus 10.22 [QD basal insulin] events per 100 PYE). Likewise, the proportions of subjects reporting AEs were similar in both treatment groups (5.1% versus 5.3%). The majority of events were non-serious and mild, while the outcome for the majority of events was 'not recovered'. The investigators judged the vast majority of «diabetic retinopathy or maculopathy» events (95 of 111 and 104 of 114) as unlikely related to the trial product.

5. Hyperglycaemia including diabetic ketoacidosis (DKA)

Another aspect of the PD profile of Ico QW is that the trough level at the end of the dosing interval is expected to be lower than with a QD basal insulin. Hence, coverage of basal insulin may become inadequate (insufficient) in the days prior to weekly dose administration and shortly thereafter, with a negative impact on glycaemia during this time window.

The overall rate [events per 100 PYE] of AEs of hyperglycaemia or DKA in the Phase 3 pool was not increased in patients treated with Ico QW compared with QD basal insulin (0.66 vs. 1.38). The most frequently reported preferred term (PT) within the MedDRA search was «hyperglycaemia», being reported by 6 (0.3% [0.48 events per 100 PYE]) and 14 (0.6% [0.92 events per 100 PYE]) subjects in the Ico QW and the QD basal insulin groups, respectively.

In the T1D population (ONWARDS 6), only 2 AEs of hyperglycaemia including DKA occurred, both in the active comparator group.

The findings for the time above glycaemic range (TAR) assessed in ONWARDS 1, 2, 4 and 6 during the last 4 four weeks of the treatment period are shown below. A statistically significant difference in favour of treatment with Ico QW was observed only in ONWARDS 1, where TAR was 26.86% versus 32.27% (ETD [95 CI] of -4.58 [-6.99, -2.17]).

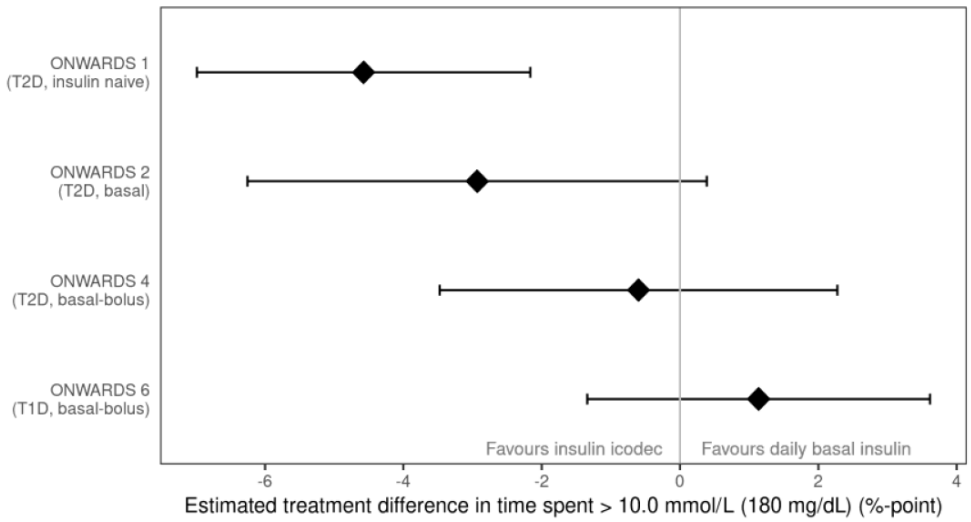


Figure 3-9

Time spent > 10.0 mmol/L (180 mg/dL) (%) at planned end of main treatment period

6. Hypokalaemia

Insulin products are known to induce clinically relevant shifts in potassium from the extracellular to the intracellular space. Only very few hypokalaemia AEs occurred in the T2D population, and no events occurred in the T1D population. Thus, the risk of hypokalaemia in Ico QW-treated patients can be assumed not to exceed the risk seen with common QD basal insulin analogues.

7. Other microvascular complications

Microvascular complications, including diabetic nephropathy are a known feature of the disease. The data from the ONWARDS programme available provide no hint of an increased risk of other microvascular diabetic complications (peripheral vascular disease and renal impairment) for Ico QW versus other QD basal insulin analogues.

8. ***Peripheral oedema***

Peripheral oedema is commonly considered a class effect when using insulin products. There were slightly higher incidences (1.1% versus 0.6%) and event rates (1.57 versus 0.87 per 100 PYE) of peripheral oedema in the patients treated with Ico QW, compared with patients who received QD basal insulin. While this pattern appeared to be consistent across the T2D and T1D populations, the clinical meaning of these subtle differences remains uncertain.

9. Lipodystrophy and local amyloidosis

Lipodystrophy is a known unwanted effect of insulin therapy, with potentially serious consequences (erratic insulin absorption from the subcutaneous depot).

Three events of lipodystrophy were reported for the Phase 3 pool: 1 event of acquired lipodystrophy in the Ico QW group (0.05 events per 100 PYE and 0.0% of subjects) and 2 events of lipohypertrophy in the QD basal insulin group (0.13 events per 100 PYE and 0.1% of subjects). All events were non-serious and mild in severity. Investigators judged the event in the Ico QW group as probably related to the trial product and the two events in the QD basal insulin group as unlikely or possibly related to the trial product, respectively.

It is notable that no AEs of lipodystrophy occurred in the T1D population (ONWARDS 6).

In conclusion, no increased risk of lipodystrophy in the Ico QW-treated patients can be implied from the distribution of the few events of lipodystrophy reported. A larger safety database is required to ultimately confirm this conclusion.

Likewise, there were no events of localised amyloidosis across the Phase 3 trials.

10. Injection site reactions

Injection site reactions are AEs typically associated with injectable drugs. As such, they must be considered a class effect of all insulin products. The question related to Ico QW is whether the U700 formulation has an impact on the rate of injection site reaction AEs. The rates observed in the Phase 3 pool would support such a conclusion: 6.04 (Ico QW) versus 3.97 (QD basal insulin). Reassuringly, these events clustered in a few patients (as evidenced by comparable incidences in both treatment arms: 1.9 versus 1.7). Moreover, none of injection site reactions in Ico QW-treated patients was serious. Finally, there was also no rise in the rate of unresolved cases without recovery in comparison with the active control (0.09 events per 100 PYE in both groups).

11. Hypersensitivity

The rate of hypersensitivity reactions was not increased in patients treated with Ico QW (6.20 versus 7.47 events per 100 PYE in the QD basal insulin group). No PTs reported occurred in >1% of the participants. PTs reported with a frequency ≥0.5% included rash, eczema, dermatitis contact, urticaria and medical device site dermatitis, all essentially evenly distributed between the treatment groups.

The incidence of hypersensitivity reactions was lower in the T2D pool compared with the Phase 3 pool, again without a meaningful imbalance between the treatment groups (3.1% [Ico QW] versus 3.8% [IDeg QD]).

Hypersensitivity reactions were more frequent in the T1D population, but still with comparable incidences across treatment groups (8.3% [Ico QW] versus 8.6% [IDeg QD]).

The analysis of investigator-reported systemic hypersensitivity reactions yielded slightly different results, with a numerical increase in the Ico QW group (0.89 versus 0.52 events per 100 PYE in the QD basal insulin group). However, there were no disturbing differences with regard to severity and outcome.

Taken together, the data show a potential for hypersensitivity reactions in patients treated with Ico QW. The intensity of these reactions in comparison with QD basal insulins appears acceptable.

12. Immunogenicity

The immunogenic potential of Ico QW has to be anticipated as substantial, given that it is a protein-based drug and previous findings with other insulin analogues. In line with this, the Phase 2 (4383) and Phase 3 (ONWARDS 2 - 4, 6) trials consistently observed anti-insulin Ico antibodies in a large fraction of Ico-treated patients. Across trials, between 59.6% and 79.2% (in insulin-naïve patients) of the subjects were positive for anti-insulin Ico antibodies (ADA) at any time on-trial which exceeded, to some extent, the corresponding numbers reported recently for IGlar preparations[10]. A matter of uncertainty is the assay specificity. In fact, cross-reactivity with human insulin was common among patients positive for anti-insulin Ico antibodies (66.7% to 77.4%).

It is noteworthy that across all Phase 3 trials, there were no events of ADA formation causing reduced clinical efficacy. Moreover, a safety correlation analysis suggested that the ADA titre had no impact on the rate of severe (level 3) or clinically significant (levels 2) hypoglycaemia across Phase 3 trials.

13. Body weight

Owing to the heterogeneity of the study populations, the summaries of the change in body weight (BW) are presented separately for all the Phase 3 trials.[11]

ONWARDS 4	2.73	2.16	0.57	[-0.39 ; 1.54]	0.2444
ONWARDS 5	2.28	1.45	0.83	[-0.37 ; 2.02]	0.1747
ONWARDS 6[a]	1.29	1.01	0.28	[-0.37 ; 0.92]	0.4060

Table 4-1 from Module 2.7.4
Change in body weight from baseline to end of treatment
FAS

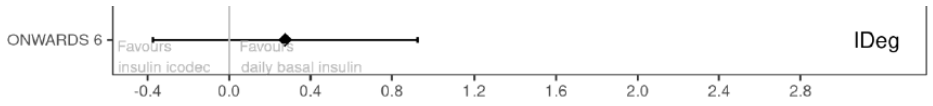


Figure 4-1 from Module 2.7.4
ETD for the change in body weight from baseline to end of treatment
FAS

In conclusion, the ETDs for the change in BW were negligible in the ONWARDS programme. The largest ETD [95% CI] was observed in the ONWARDS 2 trial (1.7 kg [0.76, 2.63]).

14. Medication errors and drug abuse or misuse

Medication errors constitute a major concern associated with insulin treatment. The following two aspects related to Ico QW treatment further reinforce this concern: the dose strength of the solution (U700) and the “single time” use of an additional loading dose when switching from previous QD basal insulin analogues.

The rates (per 100 PYE) of medication error AEs were 3.34 and 2.77 in the Ico QW group and the QD basal insulin group, respectively. One SAE of product administration error (double dose) was reported in the Ico QW group. The number of events judged by the investigator as probably related to the trial

[10] Wang, W., et al., Immunogenicity of LY2963016 insulin glargine and Lantus® insulin glargine in Chinese patients with type 1 or type 2 diabetes mellitus. Diabetes Obes Metab, 2022. 24(6): p. 1094-1104.

[11] Differences in insulin treatment regimen, prior exposure to insulin and the type of diabetes are all thought to have an impact on the change in BW.

product were 19 out of 40 events in the Ico QW group. The most frequently reported PTs in the Ico QW group were accidental overdose (15 versus 5 events in the QD basal insulin group).

Overdose and dosing error events (25 events for the PTs «accidental overdose», «prescribed overdose», «overdose», «incorrect dose administered», and «extra dose administered») clustered in the period from the first and second administration of the drug across all the trials which, per the protocol, used a loading dose when initiating treatment.

However, none of these events resulted in severe (level 3) hypoglycaemic episodes.

6.5 Final clinical benefit risk assessment

Beneficial effects and respective uncertainties

Once-weekly insulin icodec (Ico QW) showed robust glucose-lowering efficacy in patients with T2D across various stages of the disease.

In the T1D population, once-weekly insulin icodec (Ico QW) showed glucose-lowering efficacy comparable with that of once-daily basal insulin.

Unfavourable effects and respective uncertainties

The results from the ONWARDS programme suggest an increased risk of hypoglycaemia in patients with T2D and in patients with T1D. In line with this, the time spent <3 mmol/L was increased for Ico QW compared with QD basal insulin with estimated treatment ratios [95% CI] of 1.27 [0.94, 1.71] (ONWARDS 1 – T2D insulin-naïve), 1.37 [0.92, 2.04] (ONWARDS 2 – T2D treated basal insulin), 1.20 [0.91, 1.58] (ONWARDS 4 – T2D treated with basal-bolus insulin regimen), and 1.46 [1.16, 1.85] (ONWARDS 6 – T1D), respectively.

Reassuringly, there was no increased risk of severe (level 3) hypoglycaemic events for Ico QW in the T2D population. In the T1D population, severe (level 3) hypoglycaemic events were more frequent in patients treated with Ico QW than those treated with QD basal insulin. The additional (excess) events were clustered in a few vulnerable patients.

The risk of hypoglycaemia showed an apparent peak between days 2 and 4 after administration of Ico QW, mirroring the PK/PD profile.

While no obvious imbalance between treatment groups was observed for neoplasms, the database available appears too small to make any final conclusions. In this context, it is not fully transparent how investigators judged the possible relationship of the events with the basal insulin. The response to LoQ clarified that the relationship of any AEs was judged according to general instructions defined in the study protocols. No specific rules applied in case of neoplasm AEs. The results of the updated safety analysis were consistent with the earlier results.

Peripheral oedema is commonly considered a class effect when using insulin products. The data presently available suggest higher incidences (1.1% versus 0.6%) and event rates (1.57 versus 0.87 per 100 PYE) of peripheral oedema in the patients treated with Ico QW compared with patients who received QD basal insulin. The clinical meaning of these subtle differences observed consistently across the T2D and T1D populations remains unclear. Based on the updated safety analysis, the incidence and rates of peripheral oedema were comparable in both treatment arms.

Injection site reactions are considered a class effect of all insulin products. The question related to Ico QW is whether the U700 formulation has an impact on the rate of injection site reaction AEs. The rates observed in the Phase 3 pool would support such a conclusion: 6.04 (Ico QW) versus 3.97 (QD basal insulin). The clinical consequences are somewhat uncertain: events clustered in a few patients (as evidenced by comparable incidences in both treatment arms: 1.9 versus 1.7), none of the injection site reactions in Ico QW-treated patients was serious, and there was no rise in the rate of unresolved cases without recovery (0.09 events per 100 PYE in both groups). Data provided with the response to the LoQ argue against a causal link between immunogenicity and «injection site reaction» AEs.

As the Applicant did not address the question about the clinical meaning of the differences in the rates of «injection site reaction» AEs observed in the Phase 3 pool between Ico QW and QD basal insulin, the inclusion of a corresponding warning appears to be appropriate.

Ico QW caused prominent immunogenicity, as might be expected for this type of molecule. Uncertainties relate to the specificity of the assay performed. Anti-insulin Ico antibodies (ADA) had apparently no critical impact on the drug's efficacy and safety profiles. Some uncertainties relate to the correlation between the ADA-status and the risk of injection site reactions. Data provided with the response to the LoQ argue against a causal relationship between immunogenicity and «injection site reaction» AEs, although a convenient presentation of the distribution of the number and severity of «injection site reaction» events in individual patients by ADA titres is still lacking.

Benefit-risk balance

Ico QW is feasible to cover the demand in basal insulin using one injection per week. Efficacy outcomes with Ico QW were similar or better to QD basal insulin in patients with T2D. Efficacy outcomes with Ico QW were less favourable in patients with T1D, though non-inferiority for the change in HbA_{1c} was met in this population as well.

Generally, the safety profile of Ico QW is consistent with that of other basal insulins administered daily. However, Ico QW bears an increased risk of hypoglycaemia compared with QD basal insulin. As expected from the PK/PD features of Ico QW, this risk follows a weekly pattern (i.e., is related to the dosing interval). It is far more prominent in patients with T1D than in patients with T2D. Likewise, an increased risk of hyperglycaemia at the end of the dosing interval appears to be clinically meaningful only in patients with T1D.

The benefit risk ratio is judged positive for T2D.

The benefit risk ratio can be judged positive for T1D given that the information for healthcare professionals informs treating physicians, caregivers and patients in detail on the weekly pattern (peak) in hypoglycaemia risk, and the treatment is primarily limited to patients who lack an increased risk for hypoglycaemia and fail adherence to their current insulin regimen.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Awiqli FlexTouch was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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

AWIQLI® (Insulin icodec)

Composition

Active substances

Insulinum icodecum (genetically engineered using recombinant DNA technology in *Saccharomyces cerevisiae*).

Excipients

Glycerolum, Metacresolum, Phenolum, Zinci acetas, Natrii chloridum, Acidum hydrochloridum (for pH adjustment), Natrii hydroxidum (for pH adjustment), Aqua ad iniectabile pro 1ml.

The solution for injection contains 0.46 mg/mL sodium.

Pharmaceutical form and active substance quantity per unit

Awiqli® is presented as a clear and colourless solution for subcutaneous injection (s.c.) in a pre-filled pen. 1 ml injection solution contains 700 units insulin icodec. Each pre-filled pen contains 700, 1050 or 2100 units of insulin icodec in 1, 1.5 or 3 mL solution, respectively.
One (1) unit of insulin icodec corresponds to one (1) unit of insulin glargine (100 units/mL), one (1) unit of insulin detemir, one (1) unit of insulin degludec, or one (1) international unit of human insulin.

Indications/Uses

Treatment of diabetes mellitus in adults.

Dosage/Administration

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.
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 combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin (see “Clinical Efficacy”). When starting therapy with this medicinal product, it is recommended to reassess the need for or the dosing of glucose-lowering agents such as sulfonylureas and meglitinides.
In patients with type 1 diabetes mellitus, this medicinal product must be combined with bolus insulin to cover mealtime insulin requirements.

Documentation of the batch number

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage

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.

Initiation of treatment

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 mellitus

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. Depending on the

patient's glycaemic control and treatment goals, at the initiation of the switch, a one-time additional dose of Awiqli® increased by 50% may be administered (i.e., the initial dose would then be, as illustrated in table 1, 1.5 times the previous daily basal insulin dose x 7, rounded to the nearest 10 units). When assessing the potential need for a one-time additional dose, the risks of hypoglycaemic events (including through medication errors) should be weighed against temporary worsening of glyacemic control (hyperglycaemia) (see "Warnings and Precautions").

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 of the previous basal insulin 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 a one-time additional dose of Awiqli®, medication errors may occur during the subsequent injection in week 2 (see "Warnings and Precautions" section). Furthermore, dose 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 mellitus and type 1 diabetes mellitus patients, in case initially (week 1) a one-time additional dose is administered

Previous total daily dose of once- or twice-daily basal insulin (units)	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 plus 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

Missed Dose

If a dose is missed, it is recommended that it is administered as soon as possible. If this is done within 3 days of the regular administration day, the subsequent dose can be administered according to the previous weekly dosing schedule (on the usual day of the week). If there is a delay of more than 3 days, the weekly dosing schedule should be shifted to the day when the missed dose was taken. Patients who wish to go back to their original dosing day 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.

Special dosage instructions

Elderly patients

Awiqli® can be used in elderly patients. More frequent glucose monitoring is recommended. Therapeutic experience in patients ≥ 75 years of age is limited (siehe Rubrik «Pharmakokinetik»).

Patients with renal disorders

Awiqli® can be used in renal impaired patients. In patients with renal impairment, more frequent glucose monitoring is recommended (see «Pharmacokinetics»).

Patients with hepatic disorders

Awiqli® can be used in hepatic impaired patients. In patients with hepatic impairment, more frequent glucose monitoring is recommended (see «Pharmacokinetics»).

Children and adolescents

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

Mode 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 “Warnings and precautions”).

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 “Warnings and precautions”).

For further information before administration see section «Instructions for handling» in chapter «Other information».

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in “Composition”

Warnings and precautions

Hypoglycaemia

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see «Interactions», «Undesirable Effects» und «Overdosing»). The risk of hypoglycaemia with Awiqli® fluctuates throughout the dosing interval, corresponding to the weekly profile of its glucose-lowering effect, which reaches its maximum approximately 2-4 days after each weekly injection (see “Description of specific adverse reactions and additional information” in “Undesirable effects” and “Pharmacodynamics” in “Properties/Effects”).
Patients who initially receive a one-time additional dose of Awiqli® (see “Dosage/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. 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 «Interactions»).

For type 1 diabetes mellitus patients treated with Awiqli®, higher risk of hypoglycaemia could occur. If a type 1 diabetes mellitus 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 Awiqli® 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. When switching patients with type 1 diabetes to Awiqli®, patients who do not receive a one-time additional dose of Awiqli® at initiation of treatment could be at risk of transient hyperglycaemia in the first weeks.

Furthermore, concomitant illness that increase insulin requirements (e.g., infections) may lead to hyperglycaemia.

Marijuana use can potentially cause impaired glucose tolerance (other illegal substances have not been tested).

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 «Undesirable Effects»).

Switch between other insulins and Awiqli®

Switching a patient between another type, brand or manufacturer of insulin and Awiqli® should be done under medical supervision and may result in the need for a change in dosage (see «Dosage/Administration»).

During switch from daily basal insulin to weekly Awiqli® medication errors can occur in the form of e.g., overdose or dosing errors. These errors might result in hypoglycaemia or hyperglycaemia (see “Hypoglycaemia” and “Hyperglycaemia” sections under “Warnings and Precautions”). Close glucose monitoring is therefore recommended during the switch and in the following weeks.

Patients who initially (1st week) received an additional dose may forget to withhold this extra dose during the next injection (2nd week). Therefore, patients receiving the one-time additional dose must be instructed to check that they inject the correct dose, especially for the first and second injections (see «Dosage/Administration» and «Overdosing»).

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 Awiqli® 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.

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 Awiqli® is considered. If the combination is used, patients should be observed for signs and symptoms of congestive heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Sodium

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

Interactions

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

Insulin requirement may be reduced by substances that improve insulin action (increase insulin sensitivity), increase insulin secretion, inhibit hepatic gluconeogenesis, or influence intestinal glucose absorption. If the amount of insulin remains the same there is an increased risk of hypoglycaemia due to the simultaneous intake/use of:

Oral antidiabetic drugs; GLP-1 receptor agonists; ACE inhibitors (such as captopril and enalapril); Antiarrhythmic drugs like disopyramide; α-blockers and clonidine; SSRIs; Fenfluramines; MAO inhibitors; Tricyclic antidepressants; Salicylates and (rarely) other NSAIDs; Fibrates; Tetracyclines; Pentamidine (hypoglycaemia, occasionally followed by hyperglycaemia); Antimalarial drugs (quinine, chloroquine, mefloquine); Sulfonamides (such as cotrimoxazole); Cimetidine and ranitidine.

The insulin requirement may be increased if the following substances or substance groups are taken/used at the same time:

Oral contraceptives and other estrogen or progestogen preparations; Corticosteroids and ACTH; GH (Somatotropin); Danazol; Thyroid hormones; Sympathomimetics (especially β_2-sympathomimetics like ritodrine, salbutamol, terbutaline, but also α-selective sympathomimetics, as well as non-selective sympathomimetics like epinephrine); Diazoxide; Nicotinic acid and derivatives; Chlorpromazine (especially at high doses) and other phenothiazine derivatives; Diuretics (such as thiazide diuretics, indapamide, and furosemide); Antiretroviral substances; Immunosuppressive substances (ciclosporin, tacrolimus, sirolimus), Atypical antipsychotics.

The insulin requirement may be either increased or decreased depending on the dose when using the following substances:
Derivatives of lanreotide, octreotide and salicylic acid; Lithium salts (rarely).
β-blockers can lead to increased insulin resistance but can also, in certain cases, cause hypoglycaemia. Additionally, the warning symptoms of hypoglycaemia may be attenuated or masked.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

The results of the in vitro protein binding studies demonstrate that there is no clinically relevant interaction between insulin icodec and palmitate, the most abundant fatty acid in human blood. The likelihood of interaction with other protein-bound medicinal products is low.

Pregnancy, lactation

Pregnancy

There is no clinical experience with use of insulin icodec in pregnant women.
Animal studies with insulin icodec have shown adverse effects on embryofoetal development that are considered to be secondary to maternal hypoglycaemia, and not to reflect a direct effect of insulin

icodec on the developing embryo/foetus (see “Preclinical data”). Accordingly, limited clinical relevance is seen.
The use of Awiqli® during pregnancy and in women of childbearing potential who are not using contraception is not recommended.

Lactation

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. However, insulin icodec has been detected in small amounts in the plasma of nursing young animals in animal studies. A risk to the breastfed infant cannot be excluded. Awiqli® should not be used during breastfeeding.

Fertility

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

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.

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 2170 patients were exposed to insulin icodec, 1880 with type 2 diabetes mellitus and 290 with type 1 diabetes mellitus.

The most frequently reported adverse reaction during clinical trials with insulin icodec is hypoglycaemia (see «Warnings and precaution» and «Properties/Effects»).

List of adverse reactions

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows:

"very common" (≥1/10)
"common" (≥1/100, <1/10),
"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/ 1,000)
"very rare" (<1/10,000)

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 specific adverse reactions and additional information

Hypoglycaemia

Hypoglycaemia is the most commonly observed adverse drug reaction in patients using insulin icodec (see «Warnings and precaution» and «Pharmacodynamics»).

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).

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 "Pharmacodynamics" in "Properties/Effects").

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.

Injection site reactions

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

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

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.

During the 26-week treatment periods with anti-drug antibody (ADA) sampling conducted up to 31weeks 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 taken into account 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.

Specific 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 «Properties/Effects»).

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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 Awiqli®, especially if the one-time additional dose, against recommendation, continues to be taken after the first injection (see «warnings and precautions»).

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.

Properties/Effects

ATC code

A10AE07

Mechanism of action

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

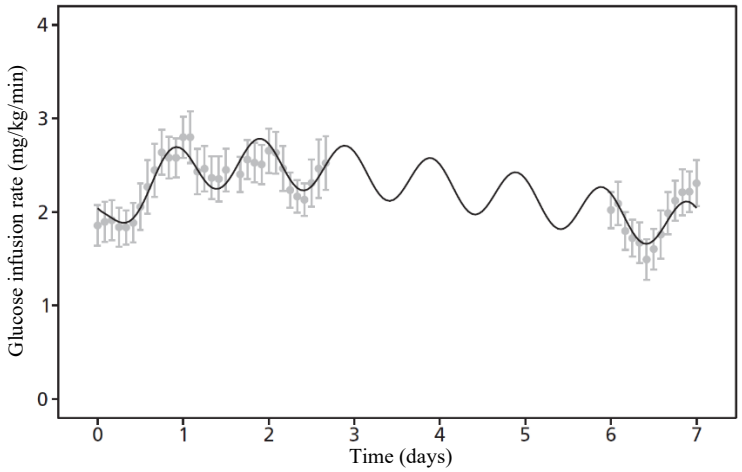
Insulin icodec binds strongly but reversibly to albumin. Thereby, a depot of essentially inactive insulin icodec is formed in the circulation and in the interstitial compartment, from which insulin icodec is slowly and continuously released and binds specifically to the insulin receptor leading to a glucose-lowering effect. In addition, insulin icodec clearance is very slow due to reduced insulin receptor binding and reduced enzymatic degradation.

Pharmacodynamics

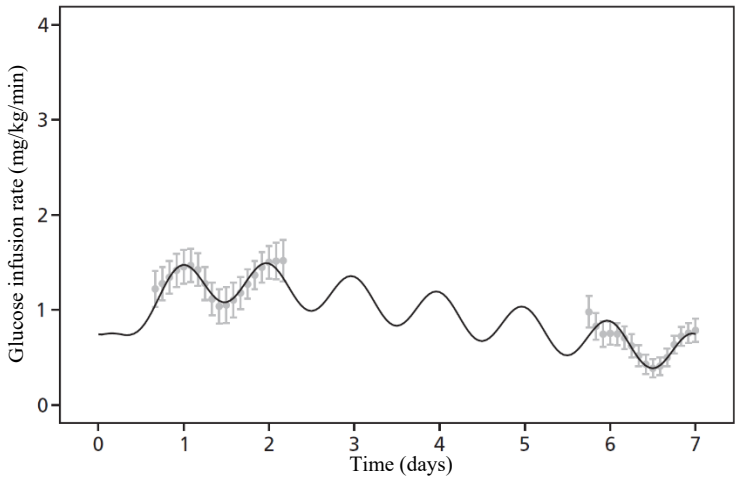
The glucose-lowering effect of insulin icodec covers the full weekly dosing interval, at clinically relevant doses. Maximum glucose lowering effect occurring during days 2-4 after injection, and a flatter pharmacodynamic profile for type 2 diabetes mellitus compared to type 1 diabetes mellitus are observed (Figure 1).

Figure 1 Full-week glucose infusion rate profile of insulin icodec at steady-state in type 2 (A) and type 1 (B) diabetes mellitus

A)



B)



Notes: Line is mean of individual model-predicted glucose infusion rate (GIR) profiles. Points and error bars are mean and 95% confidence interval of individual smoothed GIR profiles. A: type 2 diabetes mellitus GIR profile, B: type 1 diabetes mellitus GIR profile.

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.

Clinical efficacy

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 mellitus 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]*		*1.63 [1.24; 2.14]*	
< 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]	

* 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

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	**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]*	
< 7% without level 2 or 3 hypoglycaemia*	40.53	31.61

Estimated odds ratio	*1.47 [1.13; 1.92][a]*

[*] 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.

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]*	
< 7% without level 2 or 3 hypoglycaemia[*]	36.73	26.79
Estimated odds ratio	*1.59 [1.07; 2.36][a]*	

[*] 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

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]*

* Least Squares (LS) mean

Patients with type 1 diabetes mellitus

In a 26-week open-label study, with a 26-week extension part (ONWARDS 6), 582 basal-bolus treated patients with type 1 diabetes mellitus were randomised to insulin icodec and insulin degludec (100 units/mL). At baseline, the patients had a mean duration of diabetes of 19.5 years, mean HbA_{1c} of 60 mmol/mol (7.6%), mean FPG of 9.8 mmol/L and a mean BMI of 26.5 kg/m^2. The study was stratified by pre-trial basal insulin treatment (either twice daily/insulin glargine 300 units/mL or once daily) and HbA_{1c} (either < 8% or ≥ 8%) at screening (Table 7).

In this patient population, the rate of hypoglycaemia was statistically significantly higher in patients treated with insulin icodec compared to insulin degludec (Table 7).

The odds of achieving HbA_{1c} <7% were not statistically significantly different between treatment arms, treatment with insulin icodec demonstrated a non-inferior HbA_{1c} reduction compared to insulin degludec in patients with type 1 diabetes mellitus.

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]*[b]	
Time in Range (3.9-10.0 mmol/L) (%)**		
Weeks 22-26	59.10	60.85
Estimated difference	*-2.00 [-4.38; 0.38]*[b,c]	

[*] 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] no correction for multiplicity

[c] -2.00% corresponds to approximately 29 minutes less spent within range per day

Continuous glucose monitoring (CGM)

In an open-label clinical trial (ONWARDS 1), insulin-naïve type 2 diabetes mellitus 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 mellitus 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 mellitus patients.

In type 1 diabetes mellitus 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.

Paediatrics

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

Pharmacokinetics

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.

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 mellitus subjects).

Distribution

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

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.

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.

Kinetics in specific patient groups

Overall, the pharmacokinetic properties of insulin icodec using population pharmacokinetics were preserved and there was no clinically relevant difference in exposure between female and male subjects, between elderly and younger adult subjects.

The effects of renal or hepatic impairment on insulin icodec pharmacokinetics were evaluated in two open-label, parallel-group, single-dose trials. Insulin icodec exposure was slightly higher in subjects with renal or hepatic impairment compared to subjects with normal renal and hepatic function (16-21% and 13-15%, respectively). The clinical relevance of these minor differences is however limited as insulin icodec should be dosed according to individual need (see “Dosage/Administration”). Furthermore, pharmacokinetic properties of insulin icodec were preserved across a broad range of serum albumin levels (2.72 to 5.08 g/dl).

Preclinical data

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

Reproductive toxicity

In studies conducted with rats, no effects on fertility were observed with Insulin icodec; the highest exposure in animals corresponded to approximately 4.5 times (males) and 1.5 times (females) the clinical plasma exposure.

In studies conducted with pregnant rats, treatment with Insulin icodec did not result in any effects on embryofoetal development. In rabbits, abortions and increased pre- and post-implantation losses occurred at a dose associated with maternal toxicity secondary to hypoglycaemia; the exposure in the mother animals was approximately 1.7 times the clinical plasma exposure.

In a study on pre- and postnatal development in rats, adverse effects (clinical findings, reduced body weight, and mortality) were observed in the high-dose group (50 nmol/kg/day) in the nursing offspring. These effects were attributed to the presence of maternal toxicity secondary to hypoglycaemia. The exposure of the mother animals at the dose without adverse effects on the offspring (35 nmol/kg/day) was below the clinical plasma exposure.

Other information

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.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

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 the content from light.

Special precautions for storage

Keep out of the reach of children.

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 the content from light.

After first opening or if carried as a spare

For storage conditions after first opening of the medicinal product, see “Shelf life after first opening of the pen”.

Instructions for 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.

Authorisation number

69389 (Swissmedic)

Packs

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). (B)

Awiqli® pre-filled pen (FlexTouch®) containing 1050 units of insulin icodec in 1.5 mL solution.

- 1 pre-filled pen (with or without disposable NovoFine® Plus needles). (B)

Awiqli® pre-filled pen (FlexTouch®) containing 2100 units of insulin icodec in 3 mL solution.

- 1 pre-filled pen (with or without disposable NovoFine® Plus needles). (B)

Not all pack sizes may be marketed.

Marketing authorisation holder

Novo Nordisk Pharma AG, Kloten
Domicile: Zürich

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