Taiwan Food and Drug Administration

Assessment Report

Trade Name：週胰保諾特筆/
Awiqli 700units/mL solution for injection in pre-filled pen (FlexTouch)

Active Ingredient：Insulin Icodec

License Number：MOHW-BI 001287

Applicant：台灣諾和諾德藥品股份有限公司

Approval Date： 2025/04/18

Indication：治療成人糖尿病
Awiqli is indicated for the treatment of diabetes mellitus in adults

Background Information

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Active Ingredient(s)	Insulin Icodec
Applicant	台灣諾和諾德藥品股份有限公司
Dosage Form & Strengths	注射液劑 700 units/mL
Indication	治療成人糖尿病 Awiqli is indicated for the treatment of diabetes mellitus in adults
Posology	詳見仿單
Pharmacological Category **ATC Code**	A10AE07

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

General information

Insulin icodec is an analogue of insulin human where Thr^{B30} has been omitted, Tyr^{A14} has been substituted with Glu, and Tyr^{B16} and Phe^{B25} have been substituted with His. A C20 fatty acid sidechain derivative is added to the peptide backbone via the amino group in the side chain at Lys^{B29}. Insulin icodec binds to and activates the human insulin receptor.

Manufacture

Insulin icodec is manufactured using a yeast cell line. A flow diagram of the manufacturing processes is given. In addition, manufacturing steps within the processes were specified with corresponding process controls, operating ranges, and action limits. Furthermore, the sponsor has described the preparation and testing of the cell banks, testing and acceptance criteria of raw materials, and the generation the cell substrate in sufficient details. Process validations on column & membrane lifetime, hold times, and shipping were completed. Comparability results illustrated that batches of different manufacturing processes showed no significant changes on tested quality attributes.

Characterization

Primary structure and higher order structure of insulin icodec, with product- and process- related impurities from stability studies, are demonstrated.

Control of DS

The specifications of DS were provided and the acceptance criteria were justified. All batch results were within acceptable criteria to demonstrate DS quality consistency. In addition, Certification of Analysis (CoA) of the bulk drug substance shows that all test results meet specification criteria.

Stability

A shelf-life of drug substance is proposed at -20 °C ± 5°C (long-term storage condition). The long-term stability study provided test results from 5 primary batches and 3 process validation (PV) batches. All test results fall within the acceptance range. Stability studies under accelerated are also completed.

2.1.2 Drug product

Description of DP

Insulin icodec 700 U/mL (hereafter referred to as DP) is an injectable solution available in three variants. The product is intended for subcutaneous injection. The product is supplied in two cartridge sizes made of colourless hydrolytic glass (type 1 glass). The closure at one end of the cartridge is a cap that consists of a rubber disc and a seal of aluminium. The rubber disc, in contact with the drug product, is made of laminated

bromobutyl rubber (type 1 rubber). The quantitative composition, function, and quality standard of each component in the finished DP are provided. A 3% overage is present; however, overfill is applied to ensure that the nominal volume of insulin icodec variants can be withdrawn from the cartridge. For the 3 mL and 1.5 mL cartridge, the average overfill volume is approx. 0.2 mL and 0.3 mL, respectively.

Pharmaceutical Development

Insulin icodec DP composition associated with commercial manufacturing process was developed to produce a stable DP that meets the formulation, dose presentation, and DP shelf-life. The sponsor has conducted a series of studies on pH and excipients. In addition, the physical stability has been evaluated in studies simulating conditions. The drug product manufacturing process was initially established at Novo Nordisk A/S. The sponsor has described the drug product manufacturing processes at various development stages. The analytical comparability of representative insulin icodec drug product batches is demonstrated.

For microbiological attributes, Insulin icodec DP formulation contains two anti-microbial preservatives. Assurance of preservative content and effectiveness in the product are demonstrated in batch release testing and the in-use stability study, respectively.

Control of DP

The specifications of DP were provided and the acceptance criteria were justified. Test results at release are within acceptance criteria. Nine copies of CoAs of drug product batches with different presentations are provided.

Stability

A shelf-life of drug product is proposed at 5 °C ± 3°C (long-term storage condition). The long-term stability study provided test results from three representative batches each of the 1-mL, 1.5-mL, and 3-mL variants. All test results fall within the acceptance range. Stability studies under accelerated conditions is also completed.

2.1.3 Conclusion

Overall, the sponsor has provided information regarding the general properties of DS, manufacturing processes for the active substance and finished product, raw materials, controls for DS and DP, and stability studies of DS and DP. Therefore, the quality of this product is considered to be acceptable. Physicochemical and biological aspects have been investigated and are controlled in a satisfactory way.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro pharmacodynamic studies demonstrated that insulin icodec is a full agonist of insulin receptors, eliciting a biological profile comparable to human insulin. While it

induced growth-promoting effects, the relative in vitro mitogenic response was lower compared to human insulin, consistent with its lower affinity and potency. In vivo pharmacology studies revealed a glucose-lowering effect in rats, dogs, and pigs, along with reductions in HbA1c levels in rats. However, off-target studies indicated inhibition of GABAA receptors and thyroid hormone receptors at doses exceeding human exposure at a dose of 230 U/week. Safety pharmacology studies in rats and dogs showed no significant effects on the neurological, respiratory, or cardiovascular systems.

2.2.2 Toxicological Studies

Insulin icodec underwent GLP-compliant repeated-dose toxicity studies for up to 52 weeks in rats and 26 weeks in dogs via subcutaneous administration. Toxicity findings in both species primarily involved exaggerated pharmacological effects (low plasma glucose levels) and their secondary consequences, consistent with observations seen with other insulin products. These findings largely resolved during a recovery period. Notably, there was a non-dose-dependent increase in mammary gland tumors in female rats treated with insulin icodec compared to untreated controls. The incidence of mammary tumors for insulin icodec did not differ significantly from that observed with NPH insulin. The clinical relevance of these findings to humans is currently unknown. Conventional genotoxicity testings were not conducted on insulin icodec. Similar to human insulin, insulin icodec slightly increased the incidence of visceral/skeletal abnormalities in rats and rabbits at doses below the human exposure level of 230 U/week.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

After subcutaneous injection, clinical steady state was reached after 2-4 weeks when initiating insulin icodec without a one-time additional dose and after 2-3 weeks when initiating insulin icodec with a one-time additional dose of 50% with the first dose. Dose proportionality in total exposure is observed after subcutaneous administration within the therapeutic dose range. Total exposure of insulin icodec after a single dose was comparable across injection regions. The affinity of insulin icodec to serum albumin corresponds to a plasma protein binding of > 99% in human plasma. No clinically relevant differences in pharmacokinetics properties of insulin icodec are seen across serum albumin levels. Degradation of insulin icodec is similar to that of human insulin. The half-life after subcutaneous administration is approximately one week independent of dose.

2.3.2 Interaction Studies

Insulin icodec has a minor impact on regulation of CYP450 enzymes. Antidiabetic medicinal products, GLP-1 receptor agonists, sulfonylurea, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids, and sulfonamides may reduce the insulin requirement. Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol may increase the insulin requirement. Octreotide/lanreotide may either increase or decrease the insulin requirement. Alcohol may intensify or reduce the hypoglycemic effect of insulin. Beta-blockers may mask the symptoms of hypoglycemia.

2.3.3 Special Populations

The pharmacokinetic properties of insulin icodec were preserved and there was no clinically relevant difference in exposure between female and male subjects, between elderly and younger adult subjects (range of studied age of 18-86 years old), or between healthy subjects and subjects with renal or hepatic impairment. No dose adjustment is required for patients with hepatic or renal impairments.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Six phase 3a confirmatory efficacy and safety trials (ONWARDS 1-6) were provided to support the efficacy of Awiqli (insulin icodec) for the treatment of diabetes mellitus in adults. The population studied spanned insulin naïve T2D subjects (ONWARDS 1, 3, and 5), T2D subjects previously on basal insulin (ONWARDS 2) or basal-bolus regimen (ONWARDS 4) and subjects with T1D (ONWARDS 6).

The phase 3a trials were specifically designed to prospectively test for HbA1c non-inferiority against active comparators. The non-inferiority margin of 0.3% was chosen for this endpoint. Furthermore, ONWARDS 1, 2, 3 and 5 were designed to prospectively test for superiority if non-inferiority was demonstrated. ONWARDS 1, further included a superiority test on percentage of time in range (TIR).

<u>Trials with insulin naïve T2D subjects</u>

In ONWARDS 1 (NN1436-4477), estimated change from baseline to week 52 in HbA1c was -1.55%-point with insulin icodec and -1.35%-point with insulin glargine, demonstrating non-inferiority and superiority of insulin icodec vs. insulin glargine (Estimated treatment difference [ETD]: -0.19%; 95% confidence interval [CI]: -0.36%, -0.03%; p-value <0.0001 and p-value = 0.0210, respectively). Time in target range 3.9–10.0 mmol/L from week 48 to week 52 was 71.94% with insulin icodec and 66.90% with insulin glargine, demonstrating superiority of insulin icodec vs. insulin glargine

(ETD: 4.27%; 95% CI: 1.92%, 6.62%; p-value = 0.0004).

In ONWARDS 3 (NN1436-4479), estimated change from baseline to week 26 in HbA1c was -1.57%-point with insulin icodec and -1.36%-point with insulin degludec, demonstrating non-inferiority and superiority of insulin icodec vs. insulin degludec (ETD: -0.21%; 95% CI: -0.34%, -0.08%; p-value <0.0001 and p-value = 0.0016, respectively).
In ONWARDS 5 (NN1436-4481), estimated change from baseline to week 52 in HbA1c was -1.68%-point with insulin icodec with DoseGuide and -1.31%-point with once daily (OD) insulin analogues, demonstrating non-inferiority and superiority of insulin icodec with DoseGuide vs. OD insulin analogues (ETD: -0.38%; 95% CI: -0.66%, -0.09%; p-value <0.0001 and p-value = 0.0092, respectively).
Trials with T2D subjects previously on basal insulin or basal-bolus regimen
In ONWARDS 2 (NN1436-4478), estimated change from baseline to week 26 in HbA1c was -0.93%-point with icodec and -0.71%-point with degludec, demonstrating non- inferiority and superiority of icodec vs degludec (ETD: -0.22%; 95% CI: -0.37%, -0.08%; p-value <0.0001 and p-value = 0.0028, respectively).
In ONWARDS 4 (NN1436-4480), estimated change from baseline to week 26 in HbA1c was -1.16%-point with insulin icodec and -1.18%-point with insulin glargine, demonstrating non-inferiority of insulin icodec vs. insulin glargine (ETD: 0.02%; 95% CI: -0.11%, 0.15%; p-value <0.0001).
Trial with T1D
In ONWARDS 6 (NN1436-4625), estimated change from baseline to week 26 in HbA1c was -0.47%-point with insulin icodec and -0.51%-point with insulin degludec, demonstrating non-inferiority of insulin icodec vs insulin degludec (ETD: 0.05%; 95% CI: -0.13, 0.23; p-value = 0.0065).

In summary, the primary objective was met in all trials demonstrating non-inferiority of once-weekly insulin icodec versus basal insulins in both T2D and T1D, and superiority was demonstrated in the 4 trials where it was pre-specified to be tested.

2.4.2 Safety Results

A total of 2170 patients received insulin icodec in clinical trials with 1681 patient-years of exposure. Among them, 1880 were T2D and 290 were T1D patients. The most frequently reported adverse reaction in patients using insulin icodec was hypoglycemia, followed by injection site reaction and peripheral edema. The proportions of subjects with SAEs and AEs leading to treatment discontinuation were low and similar for insulin icodec and daily basal insulin. The only preferred term reported as a SAE more

than once in the T1D population was hypoglycemia. The only preferred terms, for AEs leading to permanent treatment discontinuation, reported by more than one subject with insulin icodec was weight increased, urticaria, and adenocarcinoma pancreas.

In T2D patients, insulin icodec had a higher incidence rate of clinically significant hypoglycemia (level 2; < 54 mg/dL) compared with daily basal insulin. However, subjects with severe hypoglycemia (level 3; severe cognitive impairment requiring external assistance for recovery) were few, and none of the severe hypoglycemic episodes were nocturnal. For T1D patients, there was a higher risk of level 2 or 3 hypoglycemia, including level 2 or 3 nocturnal episodes, compared to insulin degludec. However, the incidence rate of hypoglycemia did not increase over time throughout the trial, and the mean time below range (TBR) in insulin icodec group could meet the internationally recommended target. Most hypoglycemic episodes were observed on day 2-4 after weekly administration across the ONWARDS trials.

There was no increased risk of CV disorders in the insulin icodec group compared to the daily basal insulin group based on the evaluation of event adjudication committee (EAC)-confirmed CV events. Hypersensitivity reactions were reported for a similar proportion of subjects in the insulin icodec group and daily basal insulin group. Medication error was a special concern with regard to forgetting to remove the recommended one-time additional dose after the first injection.

2.5 Bridging Study Evaluation

Dose-normalized PK data in patients with type 1 or type 2 diabetes were similar in East Asian and Western populations. The ethnic difference was negligible from PK point of view.

Subgroup analyses were conducted on multi-regional clinical trials ONWARDS 2, 3, and 6 to evaluate ethnic difference in treatment response. The efficacy results were generally consistent across the overall and East Asian populations, with one notable exception in ONWARDS 6: Japanese subjects treated with insulin icodec showed a marginally less favorable HbA1c reduction compared to Japanese subjects treated with insulin degludec. The safety profile of East Asian subjects remained aligned with the overall population’s findings. The observed ethnic differences in clinical efficacy and safety were deemed not clinically significant, thereby supporting the waiver of a bridging study.

2.6 Conclusion

In summary, the primary objective was met in all ONWARDS trials, demonstrating the non-inferiority of once-weekly insulin icodec compared to daily basal insulins in both T2D and T1D populations. Moreover, superiority was established in four insulin-naïve

and basal-switch trials where such hypothesis testing was pre-specified. While T1D patients treated with insulin icodec showed a higher risk of hypoglycemia compared to those using insulin degludec, the overall benefit-risk ratio remained acceptably favorable in this patient population. Consequently, Awiqli presents a favorable risk-benefit profile for the treatment of diabetes mellitus in adults, both T1D and T2D, supporting its recommendation for regular approval.

3. Post-Marketing Requirements

N/A