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CLINICAL EVALUATION OF INSULIN ICODEC (AWIQLI®) FOR WEEKLY ADMINISTRATION IN THE TREATMENT OF TYPE 2 DIABETES: A NARRATIVE REVIEW OF EFFICACY, PHARMACOLOGY, AND PRACTICAL IMPLEMENTATION

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ABSTRACT

The treatment of insulin-dependent type 2 diabetes mellitus (T2DM) is often complicated by the psychological and logistical challenges inherent to daily subcutaneous injections. The introduction of Awiqli® (insulin icodec-abae)—a first-in-class basal insulin analog administered once weekly—offers a practical alternative. By modifying the molecular core of human insulin through the addition of a C20 icosanoic diacid side chain, insulin icodec achieves an extended half-life of approximately 196 hours via reversible binding to serum albumin. Data from the global Phase 3a clinical trial program demonstrate that weekly insulin icodec provides non-inferior—and, in several studies, superior—glycemic control (assessed by reductions in HbA1c levels and time in target range) compared to established daily basal insulins, such as insulin glargine U100 and insulin degludec. However, its ultra-long-acting pharmacokinetic profile necessitates careful clinical attention, particularly regarding the transient risk of hypoglycemia at the start of the weekly cycle and the rigidity of titration regimens. This review examines the structural pharmacology, key clinical trial data, and practical implementation strategies required to safely utilize this novel ultra-long-acting insulin in routine clinical practice.

INTRODUCTION

The timely initiation of basal insulin is essential for optimal glycemic control in type 2 diabetes. However, clinical practice is often hindered by therapeutic inertia—characterized by a delay in treatment intensification—stemming from both physician indecision and patient reluctance. Daily injections can disrupt daily life, contributing to poor adherence, missed doses, and an increased long-term risk of microvascular and macrovascular complications. Reducing the injection burden—from 365 to 52 administrations per year—has been a fundamental objective in diabetes pharmacology. The approval of insulin icodec (Awiqli®) contributes to achieving this goal. While a simplified dosing regimen may improve treatment satisfaction and adherence, an ultra-long-acting basal insulin necessitates modifications to standard approaches for dose management and titration. This review evaluates the molecular mechanism of insulin icodec, analyzes key outcomes from the ONWARDS clinical trial program, and proposes practical protocols for patient management in real-world clinical settings.[1]

Molecular Engineering and Pharmacokinetics

The design of insulin icodec is based on specific modifications to the native human insulin molecule intended to extend its activity over a full 168-hour week. Three structural adjustments are key to achieving this prolonged effect.

Amino Acid Substitutions

Substitutions at positions A14 (tyrosine replaced by glutamic acid), B16 (tyrosine replaced by histidine), and B25 (phenylalanine replaced by histidine) reduce the molecule's affinity for the insulin receptor. This modification slows down receptor-mediated clearance without compromising maximum signaling efficiency.

Fatty Acid Acylation: A C20 icosanoic diacid chain is attached to the lysine residue at position B29 via a hydrophilic spacer. This structure facilitates strong, reversible binding to human serum albumin. Following subcutaneous injection, icodec molecules bind to circulating albumin, creating an inactive reservoir within the intravascular and interstitial compartments. The slow and continuous release of the free, active monomer from this albumin reservoir produces a stable and constant hypoglycemic effect. The terminal half-life is prolonged to approximately 196 hours (7 days). Steady-state plasma concentrations are reached after three or four consecutive weekly doses, ensuring a constant basal delivery of

insulin that minimizes the daily metabolic fluctuations observed with shorter-acting analogs.[2]

Analysis of the ONWARDS Phase 3a Clinical Program:

The safety and efficacy of insulin icodec were established in the ONWARDS clinical trial program, which evaluated this weekly formulation compared to standard daily basal insulins across diverse patient populations.

Glycemic Efficacy in Insulin-Naïve Cohorts:

In the 78-week ONWARDS 1 trial, 984 insulin-naïve adults with poorly controlled type 2 diabetes (T2D) were randomized to receive either icodec once weekly or insulin glargine U100 once daily. Regarding the primary endpoint, the icodec group demonstrated a mean HbA1c reduction of 1.55%, a statistically significant improvement compared to the glargine group (1.35%). Continuous glucose monitoring (CGM) also revealed that patients treated with icodec spent significantly more time within the target range (70 to 180 mg/dL), without an increase in hypoglycemic episodes. Similarly, the ONWARDS 3 trial compared icodec with daily insulin degludec, in combination with non-insulin therapies; a mean HbA1c reduction of -1.57% was observed for icodec, versus -1.36% for degludec.[3]

Transitioning Patients from Daily Basal Insulin:

Several trials have examined the safety of switching to a weekly basal insulin regimen in patients already receiving basal insulin.

ONWARDS 2: Evaluated patients who switched from daily insulin glargine or degludec to icodec. The results confirmed the non-inferiority of icodec, and treatment satisfaction scores clearly favored the weekly injection regimen.

ONWARDS 4: Focused on complex basal-bolus regimens. Icodec maintained its non-inferiority compared to glargine U100 when combined with prandial insulin aspart, demonstrating that weekly basal administration can safely provide prandial coverage. * ONWARDS 5: Icodec was evaluated in real-world clinical settings using a digital dosing application that enabled patient-controlled titration. This trial highlighted the most significant difference compared to daily options, showing a mean HbA1c reduction of -1.68% for icodec versus -1.31% for daily analogs. These results underscore the value of combining a simplified

dosing regimen with structured digital support. Safety Profile and Hypoglycemia Considerations.[4]

While the efficacy results are positive, the prolonged action of icodec insulin necessitates careful attention to safety data.

Hypoglycemia Profiles: Across all ONWARDS trials, overall rates of severe or clinically significant hypoglycemia (Level 2/3) were low, averaging less than one event per patient-year of exposure. However, the data reveal a specific temporal pattern: hypoglycemic episodes tend to cluster between days 2 and 4 of the weekly dosing cycle. This aligns with the peak pharmacokinetics of free icodec observed at the beginning of the cycle, before the albumin reservoir gradually declines over the remainder of the week.

General Adverse Events: The overall safety profile revealed no major differences between weekly icodec and daily alternatives. Serious adverse events (SAEs)—including cardiac events or severe infections—occurred in 5% to 10% of patients across all study groups, with no evidence of product-specific toxicity. Mild injection-site reactions, transient peripheral edema, and moderate weight gain (averaging 1 to 2 kg) were observed; these manifestations are consistent with typical reactions seen upon initiating standard insulin therapy.[5]

Practical Strategies for Clinical Implementation:

Transitioning from a daily injection regimen to a weekly one requires a structured clinical protocol. Since a single dose covers an entire week, dosing errors cannot be corrected immediately.

Dosing and Titration Protocol:

Patient Selection: Identify patients with type 2 diabetes (T2D) who require optimization of their basal insulin. Avoid using icodec in patients with highly unpredictable daily schedules, severe hepatic impairment, or those planning a pregnancy.

Initial Dosing: Calculate the initial weekly dose based on the patient's previous total daily insulin requirements; use a standard weight-based protocol if the patient has not previously received insulin.

Scheduling: Determine a fixed day of the week for the injection, tailoring it to the patient's routine (e.g., Sunday morning). If a dose is missed, it may be administered up to 3 days later without altering the usual weekly schedule.

Titration: Adjust the dose once weekly based on the lowest fasting blood glucose (FBG) values recorded during the preceding 3 days. Standard adjustments involve increments of 20 to 70 units per week to avoid insulin accumulation before stable concentrations are reached.

Special Populations and Practical Management:

Renal and Hepatic Impairment: Although icodec clearance does not depend on renal filtration, patients with advanced chronic kidney disease (CKD) or hepatic dysfunction may exhibit unpredictable insulin sensitivity. Dose adjustments should be made gradually, and regular self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM) should be implemented from the start of the weekly cycle.

Perioperative Period and Intensive Care: If a patient must fast in preparation for major surgery, the 7-day pharmacokinetic profile cannot be rapidly altered. It may be necessary to administer intravenous dextrose infusions to maintain stable blood glucose levels while on a fixed weekly basal insulin dose.

Future Perspectives

The approval of insulin icodec represents a significant milestone in diabetes management; however, future clinical research and development will likely focus on several critical areas:

Extension to Type 1 Diabetes: Further research is needed to determine the safety and efficacy profiles of insulin icodec in patients with type 1 diabetes, particularly regarding the risk of severe hypoglycemia and the necessary adjustments to basal-bolus titration strategies.

Digital Health Integration:

As demonstrated by the ONWARDS 5 trial, the synergy between an ultra-long-acting insulin and digital titration tools is powerful. Future developments should aim to create standardized, interoperable digital decision-support systems that can be easily integrated with various electronic health record (EHR) platforms globally.

Long-term Real-World Evidence (RWE):

Post-market pharmacovigilance studies will be crucial for understanding the long-term safety profile of icodec in diverse patient populations that were not fully represented in clinical trials, including geriatric patients with multiple comorbidities and those with complex polypharmacy.

Economic Analyses: Comprehensive pharmacoeconomic studies are required to assess the cost-effectiveness of switching from less expensive daily insulins to icodec, considering factors such as potential improvements in treatment adherence, reduced hospitalizations, and long-term cost savings related to complications.

CONCLUSION

Insulin icodec (Awiqli®) offers a practical solution for overcoming injection fatigue and poor treatment adherence in type 2 diabetes. By utilizing albumin-mediated kinetics to ensure stable basal coverage over a one-week period, this compound achieves glycemic control that is equivalent to—or even better than—traditional daily options. The primary clinical drawback lies in the existence of a specific period at the beginning of the week during which the risk of hypoglycemia increases, as well as the inability to make rapid reductions in the daily dose. For suitable patients—particularly those using continuous glucose monitoring or who have difficulty adhering to a daily injection regimen—weekly insulin icodec simplifies diabetes management and provides an effective alternative to daily basal therapies.

REFERENCE

1. Philis-Tsimikas A, et al. Clinical use of once-weekly insulin icodec: translating clinical trial data into practical guidance for diabetes management. Novo Nordisk Science Hub / UT Southwestern Portfolio, 2025.
2. Kunzmann K. FDA approves insulin icodec (Awiqli) as first once-weekly basal insulin for type 2 diabetes. HCP Live [Internet]. 2026 [cited 2026 May 31]. Available from: https://www.hcplive.com
3. Rosenstock J, Bain SC, Gowda A, Jódar E, Liang B, Lingvay I, et al. Weekly icodec versus daily glargine U100 in type 2 diabetes without previous insulin. N Engl J Med., 2023 Jul 27; 389(4): 297-308. PubMed PMID: 37356066.
4. Nishimura E, Pridal L, Glendorf T, Hansen BF, Hubálek F, Kjeldsen T, et al. Molecular and pharmacological characterization of insulin icodec: a new basal insulin analog

designed for once-weekly dosing. BMJ Open Diabetes Res Care., 2021 Aug; 9(1): e002301. PubMed PMID: 34413121; PubMed Central PMCID: PMC8378391.

5. National Center for Biotechnology Information (NCBI). Clinical review - Insulin icodec (Awiqli). Bethesda (MD): National Library of Medicine (US); 2026 [cited 2026 May 31]. Available from: https://www.ncbi.nlm.nih.gov