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Commentary
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Navigating the Efficacy-Safety Trade-Off of Once-Weekly Insulin Icodec in Clinical Practice

Sawera Liaqat[1], Dilawaiz Liaquat[2]

[1]People's University of Medical and Health sciences for women, Nawabshah, Sindh Pakistan.

[2]Baqai Medical University, Karachi, Pakistan

[1]Corresponding Author Email: saweraliaqat925@gmail.com

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Clinical commentary

On 26 March 2026, the US Food and Drug Administration (FDA) approved Awiqli® (insulin icodec-abae) injection 700 units/mL—the first once-weekly basal insulin indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2D). This approval represents the first new class of basal insulin to reach US patients in more than two decades. Therapeutic inertia and suboptimal adherence remain persistent barriers to optimal glycemic control in T2D. By reducing the frequency of basal insulin injections from 365 to 52 per year, icodec offers a simpler regimen that may address both concerns. However, icodec's extended half-life of approximately 1 week introduces pharmacokinetic considerations with direct implications for hypoglycemia risk. The benefit-risk profile of icodec, therefore, warrants careful individualized evaluation as clinicians integrate this agent into routine clinical practice.

Efficacy Evidence from the ONWARDS Trial Program

The phase 3a ONWARDS clinical trial program evaluated icodec across six global randomized controlled trials enrolling more than 4,000 adults with T1D or T2D. In insulin-naive individuals with T2D, ONWARDS 1 (n = 984) demonstrated that icodec reduced HbA1c by an estimated 1.55 percentage points from a mean baseline HbA1c of 8.5%, compared with 1.35 percentage points with insulin glargine U100 (estimated treatment difference: −0.19 percentage points; 95% CI: −0.30 to −0.08; $p < 0.001$), with icodec also significantly increasing time in range (71.9% vs. 66.9%). The study was open-label and treat-to-target in design, with weekly doses titrated in 20-unit increments to a fasting plasma glucose target of 80–130 mg/dL.

ONWARDS 3 (n = 588), a 26-week, double-dummy, randomized trial of insulin-naive T2D patients, confirmed a 0.20 percentage-point HbA1c advantage over once-daily insulin degludec (HbA1c reduced from 8.6% to 7.0% with icodec versus 8.5% to 7.2% with degludec; $p < 0.001$). A participant-level meta-analysis of ONWARDS 1–5 (n = 3,765) further established that icodec produced a small but consistent reduction in HbA1c versus once-daily comparators, with rates of combined clinically significant or severe hypoglycemia that were not statistically significantly different in terms of incidence (17.9% vs. 16.2%; OR

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1.14, 95% CI 0.94–1.38; p = 0.18), though the episode rate was modestly but significantly higher with icodec (1.15 vs. 1.00 episodes/participant-year; estimated rate ratio 1.51, 95% CI 1.24–1.85).

Hypoglycemia: A Clinically Significant Safety Signal

The efficacy advantage of icodec is accompanied by a clinically significant safety signal that warrants careful consideration. In ONWARDS 1, combined clinically significant (level 2) or severe (level 3) hypoglycemia occurred at rates of 0.30 versus 0.16 events per patient-year with glargine U100. This difference was statistically significant in ONWARDS 3 (0.35 vs. 0.12 events per patient-year; p = 0.01). Across the ONWARDS program, level 1 hypoglycemia rates were consistently higher with icodec, with rate ratios ranging from 1.25 to 1.88. Combined level 2/3 hypoglycemia was elevated by 71– 89% in three of the six trials. Despite icodec's extended half-life, absolute hypoglycemia rates in insulin-naive T2D populations remained below 1 episode per patient-year, and the duration of individual hypoglycemic episodes was not prolonged. ONWARDS 6 demonstrated substantially higher hypoglycemia rates in type 1 diabetes, which appropriately informed the FDA's decision to restrict approval to T2D.

Clinical guidance: Patient selection and Dosing

Post hoc analyses from ONWARDS 1–5 inform practical patient selection. In the insulin-naive T2D population, icodec's weekly dosing offers both a reduction in injection burden and a favorable absolute hypoglycemia profile. Absolute rates of combined level 2/3 hypoglycemia in this group remained below 1 episode per patient-year, supporting the use of this group as an appropriate starting population for insulin-naive patients.

Patients currently receiving multiple daily injections or continuous subcutaneous insulin infusion represent a higher-risk subgroup. ONWARDS 4, which enrolled insulin-experienced T2D patients already on basal-bolus therapy, demonstrated a higher rate of icodec-related hypoglycemia, which was observed more frequently than in insulin-naive populations, and this cohort requires individualized benefit-risk assessment.

With respect to older patients, a post hoc analysis of ONWARDS 1–5 stratified by age (≥65 years, 55–64 years, and <55 years) found that efficacy and hypoglycemia profiles were broadly consistent across age subgroups, with no statistically significant treatment-by-age interaction. However, given the higher inherent risk of hypoglycemia-related consequences in elderly patients, clinical vigilance remains warranted. Similarly, a post hoc renal function analysis of ONWARDS 1–5 found no statistically significant treatment interactions by kidney function subgroups for HbA1c change, with efficacy and hypoglycemia outcomes broadly consistent across categories from normal function through moderate impairment. Patients with impaired hypoglycemia awareness, regardless of comorbidity, require closer monitoring given icodec's long pharmacodynamic duration.

From an initiation standpoint, the recommended starting dose for insulin-naive patients is 70 units administered subcutaneously once weekly (equivalent to 10 units per day). When switching from a once-daily basal insulin, the approved prescribing information recommends calculating the total weekly dose by multiplying the previous daily dose by 7 and rounding to the nearest 10 units, with subsequent titration in 20-unit increments based on prebreakfast fasting glucose monitoring. The U-700 concentration of Awiqli® is substantially higher than that of standard formulations, and clear patient education on dose calculation and the fixed weekly schedule is essential to prevent dosing errors.

Conclusion

Insulin icodec expands the therapeutic options available for T2D management by delivering meaningful glycemic control with a substantially reduced injection burden. The consistent, modest elevation in hypoglycemia rates across the ONWARDS program is a real clinical consideration but does not preclude its use; it requires structured patient selection, adherence to published titration guidance, and ongoing glucose monitoring. Insulin-naive patients with T2D without hypoglycemia unawareness represent the most favorable initiating population. The benefit-risk profile of icodec in insulin-experienced patients, older adults, and those with impaired renal function warrants individualized evaluation, supported by currently available post hoc data.

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