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Once-weekly insulin icodec: pharmacology, phase 3 evidence and clinical positioning

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ABSTRACT

Insulin icodec is the first once-weekly basal insulin, and weekly dosing changes how basal insulin is started, switched and monitored. We review the molecular design, pharmacokinetics and pharmacodynamics of icodec, the phase 3a ONWARDS 1-6 programme in type 2 and type 1 diabetes, and regulatory milestones to September 2026. Literature was identified in PubMed using the terms insulin icodec, ONWARDS and once-weekly insulin. In type 2 diabetes, icodec was non-inferior in all five trials and statistically superior in four, with combined level 2 or 3 hypoglycemia below one event per patient-year in the basal-only trials; in the basal-bolus trial ONWARDS 4 rates were elevated in both arms (5.64 vs 5.62 events per patient-year), a regimen effect rather than a drug effect. In type 1 diabetes, ONWARDS 6 showed non-inferior HbA1c but about double the clinically significant hypoglycemia (19.9 vs 10.4 events per patient-year), and that indication is not approved in the United States. Time in range improved in ONWARDS 1 despite nearly identical fasting glucose, so fasting glucose alone under-detects benefit. Icodec suits insulin-naive or basal-only type 2 diabetes where adherence limits control, monitored with continuous glucose monitoring where available.

Keywords Insulin, Long-Acting; Diabetes Mellitus, Type 2; Diabetes Mellitus, Type 1; Hypoglycemia; Blood Glucose Self-Monitoring; Drug Approval

Plain Language Summary

Standard basal insulin is injected once a day. Insulin icodec is a new basal insulin injected once a week instead, which means 52 injections a year rather than 365. This review explains how the molecule was designed to last a week, what the large phase 3 trials (the ONWARDS programme) found, and who is likely to benefit. In people with type 2 diabetes, icodec lowered long-term blood glucose (HbA1c) at least as well as daily insulin, and slightly better in most studies, with low rates of serious low blood sugar in people using basal insulin alone. In people with type 1 diabetes the glucose control was similar to daily insulin, but low blood sugar was about twice as frequent, so it is not approved for type 1 diabetes in the United States. Because the dose lasts a week, a missed dose matters less than it would with daily insulin, but the weekly dose is less easy to fine-tune, so people need clear instructions and, ideally, continuous glucose monitoring.

1.0 Introduction

Diabetes affected an estimated 537 million adults worldwide in 2021, a figure projected to reach 783 million by 2045.[1] India carries a disproportionate share: the ICMR-INDIAB national survey found a prevalence of 11.4% and an estimated 101 million people with diabetes, with a further 136 million living with prediabetes.[2] Diabetes is classified into type 1, type 2, gestational and other specific types, and the distinction determines whether basal insulin is replaced alone or alongside mealtime insulin.[3] Basal insulin remains essential when non-insulin therapy no longer achieves glycemic goals,[4] yet real-world goal attainment is poor, with only about 5% to 45% of people reaching target.[5]

Daily injection burden, fear of hypoglycemia, regimen complexity and needle aversion all contribute to delayed insulin initiation and poor persistence.[1] Real-world analyses of basal insulin show that roughly half of people discontinue or become poorly adherent within a year, and that non-persistence is associated with worse glycemic control and higher acute-care use.[2,3] This is the problem a weekly basal insulin is designed to solve, and it is a problem of behavior and burden rather than of intrinsic drug potency.[4,5]

Insulin icodec is the first once-weekly basal insulin analogue to complete phase 3 development and reach the market, receiving its first approval in Switzerland in March 2024 and approval by the US Food and Drug Administration for type 2 diabetes in March 2026.[1,2] It reduces basal injections from 365 to 52 per year. This review covers its pharmacology, the full ONWARDS 1-6 program, the safety evidence, the monitoring implications, and the practical questions of initiation, switching and cost.

2.0 Physiology of Basal Insulin Replacement

Basal insulin exists to suppress hepatic glucose production between meals and overnight while permitting a controlled rise at mealtimes. Endogenous insulin secretion in a person without diabetes is pulsatile and portal, and even the best subcutaneous basal insulins fail to reproduce it: they are absorbed peripherally, they cannot be switched off, and their effect varies with injection site, blood flow, exercise and renal clearance.[1,2] The clinical target is

therefore not physiological fidelity but flat, predictable exposure with a low peak-to-trough ratio, because it is the trough that determines fasting glucose and the peak that determines nocturnal hypoglycemia.[1]

This is why half-life has been extended in successive generations of basal insulin - from protamine-based preparations through glargine U100 and detemir to degludec and glargine U300 - and why weekly dosing is the logical endpoint of that trend rather than a departure from it.[1,2] It also explains the trade-off at the heart of this review. A longer half-life flattens the profile, but it also means the dose cannot be recalled: for a daily insulin, a wrong dose corrects within a day, whereas for a weekly insulin the consequences persist for several days.[2,3]

3.0 The Case for a Weekly Basal Insulin

The clinical argument for weekly dosing rests on three observations. First, basal insulin is a background therapy: it does not need to track meals, so its pharmacokinetic profile permits long and flat exposure. Second, adherence is limited by regimen fatigue rather than by efficacy, and reducing injection frequency has improved satisfaction and persistence in other injectable classes.[1,2] Third, once-weekly non-insulin injectables are already familiar to people with type 2 diabetes, so the dosing concept requires less explanation than a new drug class usually does.[3]

Two design problems must be solved at once. The molecule has to remain in circulation for a week without producing a peak that causes hypoglycemia, and it has to do so at an injection volume comparable to existing U100 preparations. Two distinct solutions have now reached phase 3: a fatty-diacid acylated analogue with deliberately weakened receptor affinity (insulin icodec), and a single-chain insulin-Fc fusion (efsitora alfa).[1,2] This review focuses on icodec and places efsitora in context later.

4.0 Pharmacology of Insulin Icodec

4.1 Molecular Design

Insulin icodec is a re-engineered analogue derived from the oral insulin candidate OI338.[1] Three design features act together. First, a C20 icosanedioic acid is attached through a hydrophilic linker to the lysine at position B29, producing strong but reversible binding to human serum albumin; albumin affinity is about 7.5-fold and 9.5-fold higher than that of insulin degludec and insulin detemir respectively.[1,2] The albumin-bound fraction forms an essentially inactive circulating depot from which free icodec is released slowly. Second, three amino acid substitutions (A14 Tyr-Glu, B16 Tyr-His, B25 Phe-His) reduce insulin receptor binding affinity to roughly 0.03% of human insulin measured for receptor isoform A with 1.5% human serum albumin present; values of 0.3% to 0.5% have been reported under other assay conditions.[1,3,4] The B16 substitution is the critical one, because reduced receptor affinity lowers receptor-mediated clearance and therefore prolongs exposure - deliberately counter-intuitive, since medicinal chemistry usually seeks higher receptor affinity for greater potency.[1] Third, the substitutions improve stability against enzymatic degradation and increase solubility, permitting a U700 formulation whose injection volume is similar to that of once-daily U100 insulins.[5,1]

4.2 Pharmacokinetics

After subcutaneous injection the median time to maximum plasma concentration is 16 hours and the mean half-life is approximately 196 hours (8 days).[1,2] In type 2 diabetes, steady state is reached after about 3 to 4 weekly doses without a loading dose - regulatory summaries describe 2 to 4 weeks - or within 2 to 3 weeks when a 50% top-up is given with the first injection.[3,4,1] More than 99% of the drug circulates bound to plasma proteins; pharmacokinetics do not vary meaningfully with age or sex, and no dose adjustment is required in renal or hepatic impairment.[3] This last point is now supported by a dedicated study of renal and hepatic impairment that found no clinically relevant exposure differences,[5] which matters because chronic kidney disease is common in type 2 diabetes and often limits insulin choices.

4.3 Pharmacodynamics

At steady state in type 2 diabetes the glucose-lowering effect is close to evenly distributed across the dosing interval: the daily share of the weekly effect is 14.1%, 16.1%, 15.8%, 15.0%, 14.0%, 13.0% and 12.0% on days 1 to 7 (Figure 2A).[1] In type 1 diabetes the profile is less even, with approximately 14% to 20% of the weekly effect on each of days 1 to 4 and about 8% by day 7 (Figure 2B).[2] The difference matters clinically. The flatter profile in type 2 diabetes is part of why the drug is better tolerated in that population, whereas the front-loaded profile in type 1 diabetes means the first days after injection carry relatively more hypoglycemia risk.[2,3]

5.0 The ONWARDS Programme in Type 2 Diabetes

ONWARDS 1-5 randomized 3,765 adults with type 2 diabetes across five treat-to-target trials that span insulin-naive and insulin-treated populations, including one trial with real-world elements.[1,2] All used a non-inferiority margin of 0.3 percentage points for the change in HbA1c, and each tested for superiority as prespecified. Comparators were insulin glargine U100 in ONWARDS 1 and 4, insulin degludec in ONWARDS 2 and 3, and an investigator-chosen once-daily analogue in ONWARDS 5.[2] Key results are summarized in Table 2 and Figure 1.

5.1 ONWARDS 1: Insulin-Naive Type 2 Diabetes versus Glargine U100

This 78-week trial (52-week main phase plus 26-week extension) enrolled 984 insulin-naive adults with HbA1c 7% to 11% at 143 sites in 12 countries.[1] At 52 weeks, HbA1c fell from 8.50% to 6.93% with icodec and from 8.44% to 7.12% with glargine U100, an estimated treatment difference of −0.19 percentage points (95% CI −0.36 to −0.03), confirming non-inferiority ($P<0.001$) and statistical superiority ($P=0.02$).[1] Time in range (70-180 mg/dL) was significantly higher with icodec (71.9% vs 66.9%; difference 4.27 percentage points, 95% CI 1.92 to 6.62; $P<0.001$), equivalent to about an extra hour per day in range.[1] Combined level 2 or 3 hypoglycemia occurred at 0.30 vs 0.16 events per patient-year of exposure (rate ratio 1.64, 95% CI 0.98 to 2.75), which was not statistically significant.[1]

5.2 ONWARDS 2: Basal Insulin-Treated Type 2 Diabetes versus Degludec

In this 26-week trial, 526 adults whose glucose remained above target on one or two daily basal insulin injections were assigned at 71 sites in nine

countries.[1] HbA1c fell from 8.17% to 7.20% with icodec and from 8.10% to 7.42% with degludec (difference −0.22 percentage points, 95% CI −0.37 to −0.08), demonstrating non-inferiority (P<0.0001) and superiority (P=0.0028).[1] Body weight changed by +1.40 kg with icodec and −0.30 kg with degludec (difference 1.70 kg, 95% CI 0.76 to 2.63), and this was the only trial in the program with a statistically significant weight difference.[1,2] Combined level 2 or 3 hypoglycemia rates were 0.73 vs 0.27 events per patient-year (rate ratio 1.93, 95% CI 0.93 to 4.02), numerically but not statistically higher with icodec.[1]

5.3 ONWARDS 3: Insulin-Naive Type 2 Diabetes versus Degludec, Double-Blind

ONWARDS 3 was the only double-blind, double-dummy trial in the program, randomizing 588 insulin-naive adults with HbA1c 7% to 11% at 92 sites in 11 countries for 26 weeks.[1] HbA1c decreased from 8.6% to 7.0% with icodec and from 8.5% to 7.2% with degludec (difference −0.2 percentage points, 95% CI −0.3 to −0.1), confirming non-inferiority (P<0.001) and superiority (P=0.002).[1] Fasting glucose, weekly insulin dose and body weight did not differ significantly. Combined level 2 or 3 hypoglycemia was numerically higher with icodec from week 0 to 31 (0.31 vs 0.15 events per patient-year, P=0.11) and statistically higher from week 0 to 26 (0.35 vs 0.12, P=0.01), although both rates remained below one event per patient-year.[1] Blinding matters here because the open-label design of the other trials is the main threat to patient-reported outcome data.[2]

5.4 ONWARDS 4: Basal-Bolus Type 2 Diabetes versus Glargine U100

This 26-week trial enrolled 582 adults with long-standing type 2 diabetes (mean duration 17.1 years) at 80 sites in nine countries, all receiving a basal-bolus regimen with two to four daily injections of insulin aspart.[1] HbA1c changed by −1.16 percentage points with icodec and −1.18 with glargine U100 (difference 0.02 percentage points, 95% CI −0.11 to 0.15; P<0.0001), meeting non-inferiority but not superiority.[1] Weekly insulin use was significantly lower with icodec overall (514 vs 559 U/week), reflecting a significantly lower bolus requirement together with a significantly higher basal dose.[1,2] Combined level 2 or 3 hypoglycemia was closely matched (5.64 vs 5.62 events per patient-year; rate ratio 0.99, 95% CI 0.73 to 1.33).[1] Rates of this magnitude are expected in a basal-bolus population; the important point is that icodec did not add to them.

5.5 ONWARDS 5: Real-World Elements and a Dosing Guide App

The largest trial randomized 1,085 insulin-naive adults at 176 sites in seven countries for 52 weeks.[1] Icodec was titrated with a digital dosing guide app, whereas the once-daily comparator was titrated at investigator discretion according to local labels; the comparator arm received no app support.[1] Icodec with the app produced a greater reduction in HbA1c (difference −0.38 percentage points, 95% CI −0.66 to −0.09), confirming non-inferiority (P<0.001) and superiority (P=0.009).[1] Combined level 2 or 3 hypoglycemia was low and not significantly different (0.19 vs 0.14 events per patient-year; rate ratio 1.17, 95% CI 0.73 to 1.86), while the mean weekly insulin dose was significantly higher with icodec (227 vs 185 U/week).[2] More participants reached HbA1c below 7% without level 2 or 3 hypoglycemia (41% vs 32%).[2] Treatment satisfaction and compliance scores favored icodec,[3] and a post hoc analysis found that greater adherence to the app's dose guidance was associated with lower self-monitored glucose and lower rates of clinically significant hypoglycemia - though, as the authors note, the drug effect and the titration-support effect cannot be separated.[4,1]

5.6 Synthesis Across the Type 2 Diabetes Programme

The signal is consistent: non-inferiority in all five trials, statistical superiority in four (the three insulin-naive trials plus the basal-insulin switch trial), and no superiority in the basal-bolus population, where the comparator arm was already delivering intensive titration.[1,2,3,4,5] Two meta-analyses of the program reach the same conclusion, reporting better HbA1c reduction with icodec and comparable or slightly higher hypoglycemia depending on population.[6,7] Absolute hypoglycemia rates were low and statistically indistinguishable from comparator in every trial except ONWARDS 3 over the 0 to 26 week window, where the difference was driven entirely by level 2 events.[3] Subgroup analysis across ONWARDS 1-5 found efficacy and hypoglycemia outcomes generally consistent by race and ethnicity, which is relevant for populations under-represented in earlier insulin trials.[8] The phase 2 program that preceded this work had already shown similar glycemic control, including a 26-week double-blind trial in which HbA1c fell by 1.3 vs 1.2 percentage points (difference −0.18, 95% CI −0.38 to 0.02; P=0.08) with a higher rate of level 1 hypoglycemia.[9]

6.0 Type 1 Diabetes: ONWARDS 6

ONWARDS 6 randomized 582 adults with type 1 diabetes (HbA1c below 10%) using multiple daily injections at 99 sites in 12 countries, comparing icodec with degludec over 52 weeks, both with mealtime insulin aspart.[1] At week 26, from baseline values of 7.59% and 7.63%, the estimated mean changes were −0.47 and −0.51 percentage points (difference 0.05 percentage points, 95% CI −0.13 to 0.23), confirming non-inferiority (P=0.0065).[1] However, the rate of combined clinically significant or severe hypoglycemia was nearly two-fold higher with icodec (19.9 vs 10.4 events per patient-year; rate ratio 1.9, 95% CI 1.5 to 2.3; P<0.0001), and the difference persisted across the full 57-week evaluation period.[1] During weeks 22 to 26, time spent below 54 mg/dL sat right on the recommended ceiling of 1%.[1] One death occurred in the icodec group and was judged unlikely to be related to the trial product.[1]

7.0 Safety and Tolerability

7.1 Hypoglycemia

Hypoglycemia defines the positioning of icodec, and the pattern differs by population (Table 4). In trials where insulin was used without mealtime bolus insulin, combined level 2 or 3 hypoglycemia remained below one event per patient-year with icodec in ONWARDS 1, 2, 3 and 5, although numerically higher than comparator in most of these trials.[1,2,3,4] The basal-bolus trial ONWARDS 4 is the exception, with rates of 5.64 vs 5.62 events per patient-year, matched between treatments and attributable to the regimen rather than the molecule.[5] In type 1 diabetes the absolute rate roughly doubled.[6] A consistent feature is that the relative excess is driven by level 2 events - glucose below 54 mg/dL requiring active management - while severe hypoglycemia remained rare in all arms.[1,2,3,5,4,6] The 54 mg/dL threshold is the internationally agreed marker for clinically important hypoglycemia in trials,[7] so this distinction is not a presentational choice but the standard basis for comparison. Two phase 2 substudies are also relevant to safety messaging: double or triple doses in people with type 2 diabetes did not increase hypoglycemia risk or alter counter-regulatory hormone responses compared with glargine U100, and time below range after those excess doses was low.[8]

7.2 Beyond Hypoglycemia

Beyond hypoglycemia, the safety profile of icodec resembles that of once-daily basal insulins.[1,2] Injection-site reactions, hypersensitivity events and immunogenicity have been reported at rates similar to comparators, no new safety concerns emerged in the phase 3 program, and the most frequent adverse reactions in the approved label are hypoglycemia, hypersensitivity reactions, injection-site reactions, lipodystrophy, pruritus, rash, edema and weight gain.[3] Weight change reached statistical significance only in ONWARDS 2.[4] Because the molecule acts for a full week, hypoglycemia that does occur can be protracted, which makes structured education about recognition and rescue essential rather than optional.[5,2]

7.3 Comparative Hypoglycemia Risk of Daily Analogues

The hypoglycemia risk of icodec is best judged against the daily analogues it replaces rather than in isolation. Second-generation basal insulins were themselves developed to reduce nocturnal and severe hypoglycemia, and a cardiovascular outcomes trial of insulin degludec versus glargine U100 in people at high cardiovascular risk showed lower rates of severe hypoglycemia with degludec.[1] This matters for interpretation in two ways. Trials that used glargine U100 as the comparator - ONWARDS 1 and 4 - compared icodec against a first-generation rather than a second-generation basal insulin, which flatters the hypoglycemia profile of the comparator and makes icodec's numerical excess look larger than it would against degludec.[2,3] Conversely, the two trials that did use degludec - ONWARDS 2 and 3 - are the ones that showed a statistically significant level 2 excess, so the honest reading is that the excess is real but small in absolute terms, and that comparator choice materially affects the apparent size of the effect.[4,5]

7.4 Special Populations

Older and frailer patients deserve specific consideration, because they are the group in whom hypoglycemia carries the greatest consequence and in whom adherence problems are most common - which is also the group most likely to be offered a weekly insulin.[1,2] The trials enrolled adults with a mean age around 60 years and excluded people with recent cardiovascular events, chronic heart failure or severe renal impairment in ONWARDS 1 to 4, so the evidence in the very elderly and in multimorbidity is thin.[3,4] Renal impairment is the exception: a dedicated pharmacokinetic study found no clinically relevant differences in exposure across degrees of renal or hepatic impairment, and pooled trial analyses found consistent efficacy and hypoglycemia outcomes across kidney-function subgroups, so no dose adjustment is required.[5,3] That said, reduced insulin clearance in renal impairment increases exposure, so more frequent glucose monitoring is prudent.[3] Type 1 diabetes, pregnancy and pediatric use remain outside the approving evidence base, and icodec is not established in any of them.[6,7]

8.0 Rethinking Monitoring and Titration for a Weekly Insulin

The most consequential finding for everyday practice is not in the HbA1c data but in the continuous glucose monitoring (CGM) data. In ONWARDS 1, time in range improved by about an hour a day with icodec while fasting glucose was essentially identical between arms.[1] That is what a flatter, longer-acting basal profile should produce, and it also means that clinicians titrating by fasting glucose alone will systematically underestimate the drug's benefit.[1,2] Time in range is an established treatment target with consensus-defined thresholds, including more than 70% in range and less than 1% below 54 mg/dL,[3] and CGM improves glycemic outcomes in people with type 2 diabetes on basal insulin.[4,5] The evidence base is thinner than it should be: ONWARDS 3 collected no CGM data at all, and in ONWARDS 2 and 4 time in range did not differ significantly between groups.[6,2] The practical recommendation that follows is to prefer CGM where available, to titrate against the combination of fasting glucose and time in range, and to recheck glycemic patterns at least once across the weekly cycle.[3,5]

9.0 Beyond Icodec: Efsitora Alfa

Efsitora alfa is the second weekly basal insulin in late-stage development, built as a single-chain insulin variant fused to an Fc domain that extends exposure through Fc recycling rather than albumin acylation.[1,2] The QWINT phase 3 program has now reported non-inferior glycemic control versus degludec in type 2 diabetes and in type 1 diabetes, and versus glargine U100 in basal-bolus type 2 diabetes.[3,4,5,6] The hypoglycemia pattern is similar in direction to icodec: broadly comparable rates in type 2 diabetes, with a less favorable profile in type 1 diabetes.[4,5] Two implications follow for this review. First, the weekly-insulin class is becoming a genuine category with an internal choice rather than a single product. Second, most of the practical questions raised here - switching arithmetic, missed doses, monitoring, patient education - are class questions, not icodec-specific ones.[2,1]

10.0 Practical Use: Initiation, Switching and Missed Doses

Initiation in insulin-naive type 2 diabetes is straightforward: 70 units once weekly, equivalent to 10 units of daily basal insulin, which keeps the injection volume similar to a U100 daily insulin.[1,2] When switching from daily basal insulin, the weekly dose is calculated as the previous daily basal dose multiplied by 7, and a 50% top-up is recommended with the first injection; if the patient is prone to missing daily doses, the top-up may be omitted because it risks overestimating the true insulin requirement.[1] Steady state arrives sooner with that top-up (2 to 3 weeks rather than 3 to 4).[3,1] From the second week onward the dose is the daily dose multiplied by 7, and titration proceeds against pre-breakfast self-monitored glucose with at least three readings per week.[1] Two practical hazards deserve emphasis. Accidental double dosing is easier when a weekly-interval habit is transferred from once-weekly non-insulin injectables, and the dose cannot be withdrawn once given, so patients must be told explicitly what to do if a dose is missed or duplicated.[1,4] Titration logic also has to change, as discussed above: fasting glucose alone is an incomplete target.[2,5] Figure 3 summarizes a practical pathway.

10.1 Missed and Duplicated Doses

A weekly interval is easier to remember than a daily one, but it creates two specific failure modes. A missed dose leaves the patient with declining but still substantial insulin exposure for several days, so the correct response is to take the dose when remembered rather than to double up, and to avoid a dose late in the week if the next scheduled dose is imminent.[1,2] A duplicated dose is the more dangerous error because it cannot be withdrawn, and it is a realistic risk in patients transferring a once-weekly habit from GLP-1 receptor agonists or other weekly injectables.[1] Because the effect of an excess dose persists, these patients need a defined plan: more frequent glucose monitoring, a lower threshold for contacting the clinic, and explicit instructions on rescue carbohydrate and when to seek help.[2,1] Phase 2 data on double and triple dosing are reassuring in aggregate - hypoglycemia risk and counter-

regulatory responses did not differ from glargine U100 in that setting - but the follow-up was short and the study excluded the patients at highest risk, such as those with renal impairment.[1]

11.0 Barriers, Adherence and Cost

A weekly insulin solves one barrier - injection burden - and leaves others untouched. Persistence with basal insulin is limited by cost, health literacy, follow-up intensity and hypoglycemia fear, and the same factors will govern icodec uptake.[1,2,3] For an Indian prescriber the practical questions are sharper still. Affordability dominates: out-of-pocket costs of ambulatory diabetes care remain a substantial share of household expenditure, and the direct cost of care is a documented driver of non-adherence.[4] The weekly analogue has to compete with generic human insulin and inexpensive daily analogues on price, not only on convenience. There is as yet no Indian real-world evidence on switching, missed doses or hypoglycemia in routine care, and none in the late-presenting patient with very high insulin requirements, which is a common local phenotype.[5,6] The dosing guide app used in ONWARDS 5 is not a substitute for structured education, and where app access is unreliable the switching protocol must work on paper.[7,8] Real-world comparative data are beginning to appear from other health systems,[9] but local pharmacovigilance and pragmatic studies remain the priority.

12.0 Regulatory Status

Insulin icodec (Awiqli; Novo Nordisk) was first approved in Switzerland on 7 March 2024, followed by Canada on 12 March 2024 and the European Union in May 2024.[1] It is now approved for both type 1 and type 2 diabetes in the European Union and in several other countries including Australia, Brazil, Japan, India and South Korea, and for type 2 diabetes only in China.[2] In the United States, the FDA Advisory Committee declined to endorse approval in type 1 diabetes in May 2024,[1] that application was not approved, and the FDA subsequently approved once-weekly icodec for adults with type 2 diabetes on 26 March 2026.[3] Weekly insulin is also entering guidance: the 2026 ADA Standards of Care address icodec within the pharmacologic treatment algorithm, reflecting the shift from investigational agent to therapeutic option.[4] Regulatory milestones are summarized in Table 5.

13.0 Conclusions

Insulin icodec delivers glycemic control non-inferior to daily basal insulin across the spectrum of type 2 diabetes and superior in insulin-naive and basal-switch populations, with low hypoglycemia rates in basal-only regimens and no excess relative to comparator in a basal-bolus regimen. In type 1 diabetes the glycemic result is acceptable but the hypoglycemia penalty is not, and that indication is not approved in the United States. The remaining questions are operational rather than pharmacological: who benefits most, how to switch safely, and how to monitor and titrate a drug whose dose cannot be recalled once administered.[1,2]

14.0 Expert Opinion

Insulin icodec is best understood not as a more potent basal insulin but as a different way of delivering an unremarkable amount of basal insulin. Its HbA1c advantage over daily analogues is real but small - between 0.19 and 0.38 percentage points in the insulin-naive trials[1,2,3] - and in my view the clinically meaningful gain lies in time in range and in the 313 injections a year that disappear. The ONWARDS 1 result is the most instructive: time in range improved by about an hour a day while fasting glucose was almost identical between arms.[1] Clinicians who titrate by fasting glucose alone will therefore undervalue the drug, and where CGM is available it should be used; the absence of CGM data from ONWARDS 3 is a genuine evidence gap rather than a trivial omission.[2]

The hypoglycemia signal needs to be read carefully rather than summarized as a class warning. In type 2 diabetes the excess is small in absolute terms, is driven by level 2 events, and in the basal-bolus trial disappears entirely once the regimen is taken into account.[1,2,3,4,5] The type 1 diabetes result is different in kind: a near doubling of clinically significant hypoglycemia without any glycemic advantage justifies the FDA's decision not to approve that indication.[6,7] I would not use icodec as a first choice in type 1 diabetes, and if it is used at all it should be in someone with recurrent ketoacidosis from missed basal doses and with reliable CGM use.[8]

Three limitations of the current evidence should temper enthusiasm. First, four of the five type 2 diabetes trials were open-label, so patient-reported outcomes carry a bias risk, and ONWARDS 5 cannot separate the drug from the dosing app.[1,2] Second, trial durations of 26 to 78 weeks are short for a molecule whose steady state takes weeks to reach and whose safety story is dominated by hypoglycemia.[3,4] Third, all trials were manufacturer-sponsored, and the comparator in ONWARDS 1 and 4 was glargine U100 rather than a second-generation analogue such as glargine U300 or degludec, which lowers hypoglycemia risk;[3,5] the apparent comparator advantage in those two trials should therefore be read partly as an artefact of comparator choice, and trials of degludec and glargine U300 have documented lower severe hypoglycemia.[6]

The weekly-insulin class now has an internal choice, and icodec will not be judged in isolation.[1,2,3,4] Its practical advantages and its monitoring demands are largely class properties, which means the switching protocol, the education package and the CGM strategy matter as much as which molecule is chosen.[5]

On selection, my position is that the benefit is largest where adherence is the limiting factor. The patient who forgets or avoids daily injections, or who has never started insulin because of injection burden, is the person for whom a 0.2 percentage-point HbA1c difference understates the true gain, because in that patient the realistic alternative is not well-titrated glargine but no basal insulin at all.[1,2,3] Conversely, the patient already well controlled on a second-generation daily analogue with no adherence problem has little to gain and something to lose, since the weekly dose is harder to fine-tune and the hypoglycemia excess, though small, is real.[4,5,6] The group in between - insulin-naive, uncontrolled, willing to inject but inconsistent with daily timing - is where the evidence and the clinical need align, and it is also the group the insulin-naive trials actually studied.[7,5,8]

The research agenda that follows is narrow and practical rather than exploratory. We need trials comparing weekly with second-generation daily analogues rather than glargine U100, so the hypoglycemia comparison is fair.[1,2,3] We need CGM-based endpoints reported systematically, because the ONWARDS 1 dissociation between fasting glucose and time in range is the finding most likely to change practice and it has not been replicated across the program.[1,4] We need prospective data on missed and duplicated doses in ordinary use, since that is where the harm from a long half-life will concentrate.[5] And we need patient-reported outcomes collected under blinding, because the treatment-satisfaction advantage of weekly dosing is currently derived mainly from open-label trials.[6,7,8] None of these require a large non-inferiority study; all are answerable with pragmatic designs.

For an Indian prescriber the constraints are different again. Cost, cold-chain logistics and pen availability will determine uptake more than a 0.2 percentage-point HbA1c difference, and the affordability of a weekly analogue against generic human insulin is unresolved.[1] The priority is therefore not further confirmatory efficacy trials - the efficacy question is answered relatively completely - but local real-world evidence on switching, missed doses, hypoglycemia in routine care, and use in the late-presenting patient with high insulin requirements.[2] Post-approval pharmacovigilance, structured

education and pragmatic monitoring studies are where the next increment in patient benefit will come from, not from another non-inferiority trial.[3,4]

Transparency section

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Declaration of generative AI use. An AI assistant (Hermes Agent, model DeepSeek-V4-Flash) was used to support literature searching, verification of references against the source publications, and language editing, and to assist in drafting sections of the text. It was used to improve the accuracy of the reference list and the clarity of the English; the author reviewed and verified all content against the primary sources, approved the final text, and takes full responsibility for the manuscript.

Figure Legends

Figure 1. Estimated treatment difference in HbA1c (percentage points) with 95% confidence intervals for once-weekly insulin icodec versus the once-daily comparator in ONWARDS 1-6. Negative values favor icodec; the dashed line marks the 0.3 percentage-point non-inferiority margin.

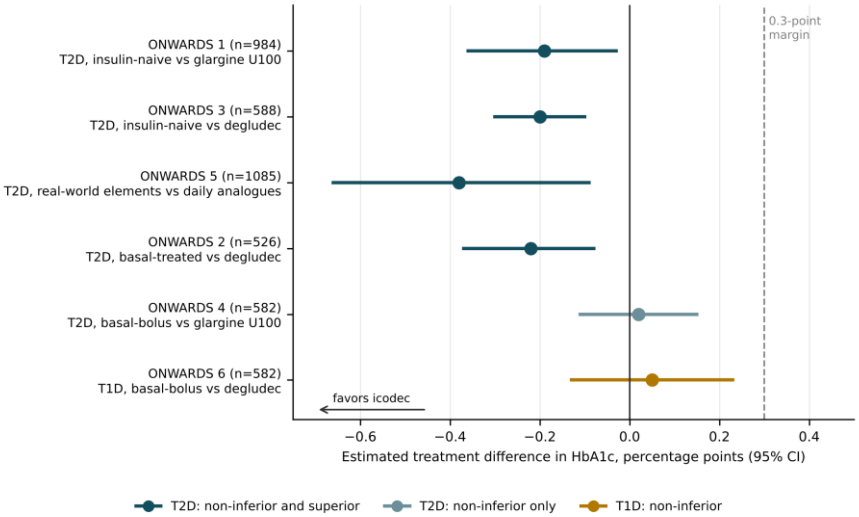


Figure 2. Share of the total weekly glucose-lowering effect delivered on each day after a once-weekly injection of insulin icodec at steady state. (A) Type 2 diabetes: 14.1%, 16.1%, 15.8%, 15.0%, 14.0%, 13.0% and 12.0% for days 1 to 7. (B) Type 1 diabetes: approximately 14% to 20% per day on days 1 to 4, falling to about 8% by day 7.

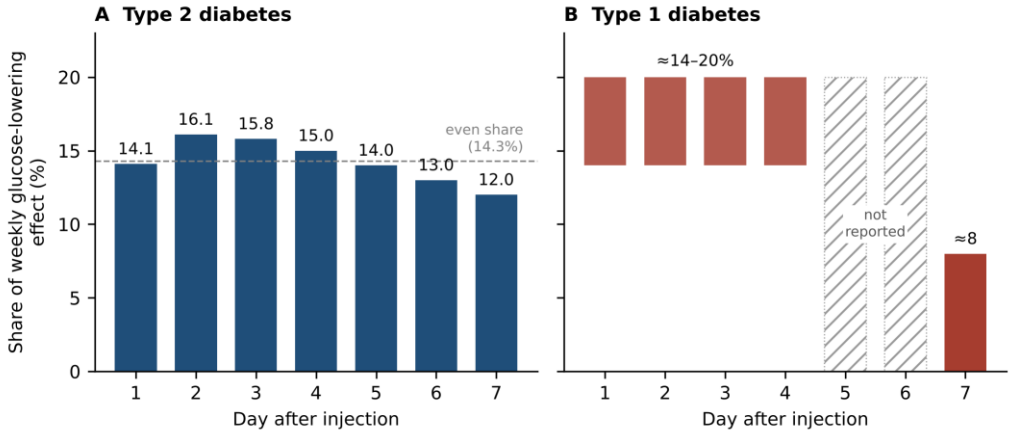
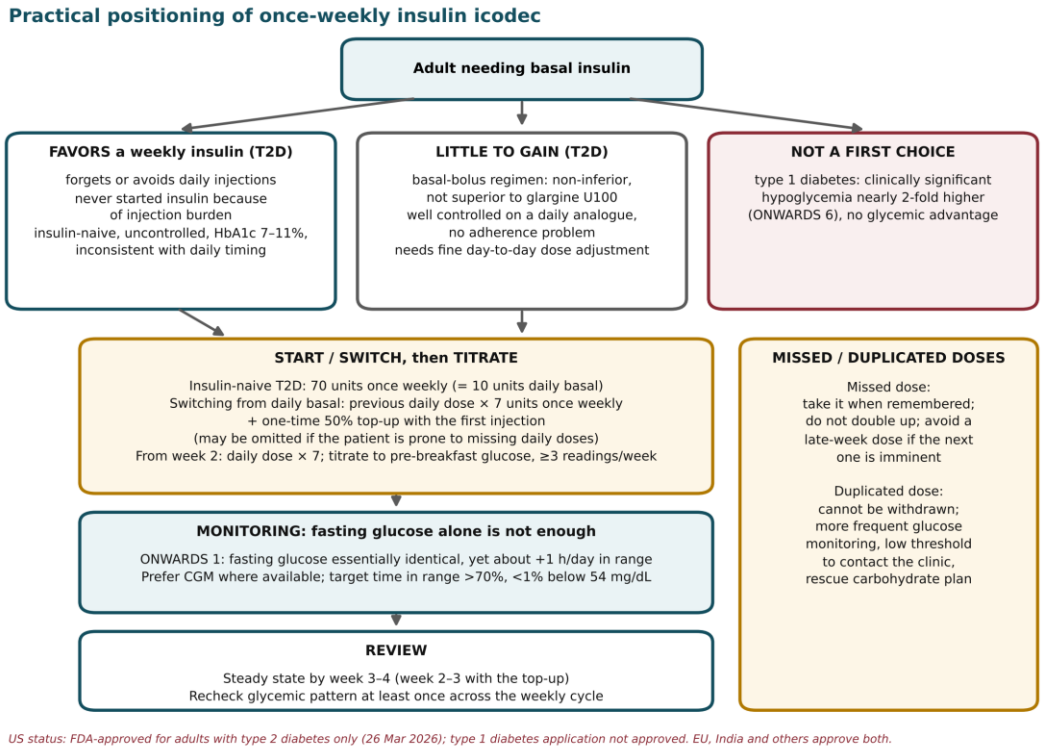


Figure 3. Practical positioning framework for once-weekly insulin icodec in type 2 diabetes: who to consider, the switching protocol, the monitoring implications, and the review schedule. CGM, continuous glucose monitoring; FPG, fasting plasma glucose.
Graphical Abstract. Visual summary of the design, type 2 and type 1 diabetes evidence, the practice implications and the regulatory timeline.



Tables

Table 1. Key pharmacological, pharmacokinetic and pharmacodynamic properties of insulin icodec.

Property	Value / description	Source
Molecular class	Acylated human insulin analogue; derived from the oral insulin candidate OI338	[6]
Amino acid substitutions	A14 Tyr→Glu; B16 Tyr→His; B25 Phe→His	[6,9]
Acylation	C20 icosanedioic acid attached via a hydrophilic linker to Lys B29	[5,6]
Albumin-binding affinity	Approximately 7.5-fold higher than insulin degludec and 9.5-fold higher than insulin detemir	[6,7]
Insulin receptor affinity	About 0.03% of human insulin (receptor isoform A with 1.5% human serum albumin); 0.3–0.5% under other assay conditions	[6,9]
Plasma protein binding	>99%	[5]
Median time to maximum concentration	16 hours	[8,9]
Elimination half-life	Approximately 196 hours (8 days)	[8,9]
Time to steady state	3–4 weekly doses without a loading dose (2–4 weeks in regulatory summaries); 2–3 weeks with a one-time additional 50% dose	[5,7,8]
Daily share of weekly effect, T2D	14.1%, 16.1%, 15.8%, 15.0%, 14.0%, 13.0%, 12.0% on days 1–7	[8]
Daily share of weekly effect, T1D	Approximately 14–20% per day on days 1–4; about 8% by day 7	[7]
Formulation	U700 (700 units/mL); injection volume	[5,6]

	similar to once-daily U100 basal insulins	
Special populations	No clinically meaningful effect of age or sex; no dose adjustment in renal or hepatic impairment	[5]
Injection sites	No clinically meaningful difference in exposure between thigh, abdomen or upper arm	[8]

Table 2. ONWARDS 1-5: design and key efficacy outcomes in type 2 diabetes.

Trial (n)	Population	Comparator	Duration	HbA1c change	ETD (95% CI), %	Hypoglycemia (level 2 or 3)
ONWARDS 1 (984)	Insulin-naive, HbA1c 7–11%	Glargine U100	78 weeks	−1.55 vs −1.35	−0.19 (−0.36 to −0.03); P=0.02	0.30 vs 0.16/PYE; RR 1.64 (0.98–2.75)
ONWARDS 2 (526)	Basal insulin-treated	Degludec	26 weeks	8.17→7.20 vs 8.10→7.42	−0.22 (−0.37 to −0.08); P=0.0028	0.73 vs 0.27/PYE; RR 1.93 (0.93–4.02)
ONWARDS 3 (588)	Insulin-naive, HbA1c 7–11%	Degludec (double-blind)	26 weeks	8.6→7.0 vs 8.5→7.2	−0.2 (−0.3 to −0.1); P=0.002	0.35 vs 0.12/PYE to week 26 (P=0.01)
ONWARDS 4 (582)	Basal-bolus, mean duration 17.1 years	Glargine U100	26 weeks	−1.16 vs −1.18	0.02 (−0.11 to 0.15); non-inferior only	5.64 vs 5.62/PYE; RR 0.99 (0.73–1.33)
ONWARDS 5 (1085)	Insulin-naive, real-world elements	Degludec, glargine U100 or U300	52 weeks	Approx. 9.0→7.2 vs 8.9→7.6	−0.38 (−0.66 to −0.09); P=0.009	0.19 vs 0.14/PYE; RR 1.17 (0.73–1.86)

Table 3. ONWARDS 6: design and key outcomes in type 1 diabetes.

Feature	Detail
Design	52 weeks (26-week main phase plus 26-week safety extension); randomized, open-label, treat-to-target, phase 3a
Population	582 adults with type 1 diabetes, HbA1c <10%, on multiple daily injections; 99 sites in 12 countries
Treatment arms	Once-weekly icodec (n=290) vs once-daily degludec (n=292), both with mealtime insulin aspart
HbA1c at week 26	−0.47 vs −0.51 percentage points; ETD 0.05 (95% CI −0.13 to 0.23); non-inferiority P=0.0065
Clinically significant or severe hypoglycemia	19.9 vs 10.4 events per patient-year; rate ratio 1.9 (95% CI 1.5 to 2.3); P<0.0001
Time below range <54 mg/dL	At the threshold of the <1% target during weeks 22–26
Regulatory consequence	US FDA Advisory Committee voted against the type 1 diabetes indication in May 2024; the application was not approved

Table 4. Hypoglycemia with insulin icodec across the ONWARDS program.

Trial	Population	Combined level 2 or 3 hypoglycemia (events/PYE)	Comparator	Rate ratio (95% CI)
ONWARDS 1	T2D, insulin-naive	0.30	0.16	1.64 (0.98–2.75)
ONWARDS 2	T2D, basal-treated	0.73	0.27	1.93 (0.93–4.02)
ONWARDS 3	T2D, insulin-naive	0.35*	0.12*	3.12 (1.30–7.51)*
ONWARDS 4	T2D, basal-bolus	5.64	5.62	0.99 (0.73–1.33)
ONWARDS 5	T2D, insulin-naive, real-world	0.19	0.14	1.17 (0.73–1.86)
ONWARDS 6	T1D, basal-bolus	19.9	10.4	1.9 (1.5–2.3)

Table 5. Regulatory milestones and practical dosing considerations.

Date or item	Detail
7 March 2024	First global approval, Switzerland, for diabetes mellitus in adults
12 March 2024	Approval in Canada
May 2024	European Union approval for diabetes mellitus in adults
May 2024	US FDA Advisory Committee votes against the type 1 diabetes indication
10 July 2024	US Complete Response Letter; type 1 diabetes application not approved
26 March 2026	US FDA approval for adults with type 2 diabetes; US launch in the second half of 2026
Other approvals	Both type 1 and type 2 diabetes in the EU and several countries including Australia, Brazil, Japan, India and South Korea; type 2 diabetes only in China
Starting dose (insulin-naive T2D)	70 units once weekly, equivalent to 10 units of daily basal insulin
Switching from daily basal insulin	Previous daily basal dose × 7 units once weekly, plus a one-time additional 50% with the first injection; the additional dose may be omitted where missed daily doses make the true requirement uncertain
Titration	From week 2, daily dose × 7, titrated against pre-breakfast self-monitored glucose with at least three readings per week; continuous glucose monitoring is preferred where available
Key counselling points	Once-weekly interval habit; avoid transferring once-weekly non-insulin injection habits; explicit instructions for a missed or duplicated dose; recognize that hypoglycemia may be protracted

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