Once-weekly basal insulin therapy in type 1 diabetes: A paradigm shift or a work in progress?

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Purpose: Type 1 diabetes mellitus (T1DM) requires lifelong basal and bolus insulin therapy to maintain glycemic control, often necessitating multiple daily injections. Recently, the development of once-weekly basal insulin formulations, insulin icodec and insulin efsitora alfa, has introduced the possibility of reducing injection burden while preserving efficacy. This review evaluates the pharmacological properties, clinical trial data, patient considerations, and regulatory landscape of these novel therapies to determine their potential role in T1DM management.

Summary: Insulin icodec and insulin efsitora alfa utilize distinct structural modifications to extend their duration of action, allowing for weekly dosing. Insulin icodec achieves prolonged activity through enhanced albumin binding and reduced insulin receptor affinity, while insulin efsitora alfa utilizes Fc-fusion technology and neonatal Fc receptor recycling. Phase 3 trials (the ONWARDS-6 trial for insulin icodec and the QWINT-5 trial for insulin efsitora), demonstrated that both insulins achieved glycemic control comparable to that provided by once-daily basal insulin degludec. However, both formulations were associated with a higher incidence of hypoglycemia, particularly during the titration period. Additionally, patient-reported outcomes varied, with insulin efsitora being associated with greater treatment satisfaction than insulin icodec.

Conclusion: Once-weekly basal insulin represents a potential paradigm shift in T1DM management, offering convenience but presenting challenges related to hypoglycemia risk, patient acceptance, and regulatory hurdles. Further research is needed to refine titration protocols, identify optimal patient populations, and address safety concerns before these therapies can become standard of care.

Keywords: basal insulin, glycemic control, insulin efsitora alfa, insulin icodec, once-weekly insulin, type 1 diabetes mellitus

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Type 1 diabetes mellitus (T1DM) is a chronic autoimmune condition characterized by the destruction of insulin-producing beta cells in the pancreas.[1] Effective management of T1DM requires both basal and bolus insulin to mimic the natural pancreatic insulin release and maintain optimal glycemic control. Unfortunately, traditional insulin regimens require multiple daily injections, which can present adherence challenges and impact patients' quality of life. Frequent injections are associated with increased physical and emotional burdens as well as potential injection site complications, making adherence to the regimen difficult for many patients.

Recently, researchers have developed once-weekly insulin formulations designed to reduce injection frequency while maintaining stable blood glucose levels.[2] Two major once-weekly insulins, insulin icodec and insulin efsitora alfa, have undergone evaluation in adults with T1DM. Early studies, such as the ONWARDS 6 trial and the QWINT-5 trial, demonstrated that weekly insulin therapies can achieve glycemic control similar to that provided by daily basal

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insulins.[3,4] However, there are concerns regarding the increased rates of hypoglycemia observed with these once-weekly formulations.

These findings suggest that while once-weekly insulin could significantly improve treatment adherence and quality of life for people with T1DM, further research is needed to refine dosing protocols and minimize hypoglycemia risk. As the Food and Drug Administration (FDA) evaluates these therapies, their potential approval could represent an important shift in T1DM management by reducing the burden of frequent injections and enhancing overall treatment adherence. This clinical review aims to evaluate the current data on once-weekly insulin therapies and discuss their potential clinical impact for patients with T1DM.

Pharmacology and medicinal chemistry

The development of once-weekly basal insulins, insulin icodec and insulin efsitora alfa, represents a significant advancement in diabetes therapy, addressing the challenge of reducing injection burden while maintaining glycemic control.[5] These novel insulins incorporate structural modifications that extend their duration of action, enabling weekly dosing while preserving efficacy (Table 1).

Insulin icodec achieves its long duration of action through enhanced albumin binding and reduced insulin receptor affinity. Similar to degludec, icodec contains an icosanedioic acid (20-carbon fatty diacid) linked to the terminal lysine through a γ -glutamyl and polyethylene glycol–like linker.[6] This hydrophobic fatty acid promotes albumin binding, leading to an extended duration of action. However, albumin alone is not sufficient to allow for once-weekly dosing. To further slow clearance, the makers of insulin icodec also introduced 3 amino acid substitutions (TyrA14Glu, TyrB16His, and PheB25His) that increase its stability and reduce insulin receptor affinity.[6] Since insulin clearance primarily occurs through insulin receptor–mediated internalization, lowering receptor binding allows insulin icodec to remain bound to albumin longer, leading to a half-life of approximately 196 hours. These amino acid changes also increase solubility, enabling icodec to be formulated at 700 U/mL, allowing for an injection volume similar to that with U100 once-daily basal insulin.[6]

Unlike icodec, insulin efsitora alfa utilizes the neonatal Fc receptor (FcRn) recycling system to extend its half-life, a mechanism that has been employed by other long-acting biologics, including etanercept and dulaglutide.[7] It exists as a covalent homodimer of a single-chain insulin (SCI) variant, where A- and B-chains are connected through a short linker and the C-terminus of each monomer is attached to the N-terminus of the Fc domain of human immunoglobulin G2.[8] This fusion allows pH-dependent recycling via the FcRn pathway, a mechanism employed by other biologics like etanercept and dulaglutide to prolong their half-life.[9] The FcRn system protects Fc-containing proteins from lysosomal degradation by recycling them back into the bloodstream in a pH-dependent manner. At acidic pH (~5.8), the Fc domain binds strongly to FcRn, preventing degradation.[10] Once the vesicle reaches the neutral pH (~7.2) of the extracellular environment, the FcRn releases its bound protein, allowing efsitora to be recycled. Additionally, multiple amino acid modifications (TyrB16Glu, PheB25His, ThrB27Gly, ProB28Gly, LysB29Gly, ThrB30Gly, IleA10Thr, TyrA14Asp, and AsnA21Gly) were introduced to facilitate the conversion of insulin to a SCI and reduce insulin receptor binding while maintaining glycemic control.[11] These modifications result in a half-life of approximately 120 hours, supporting once-weekly dosing.[11]

The structural modifications in icodec and efsitora build on the progression of basal insulin analogues developed over the past 2 decades. Early basal insulins relied on chemical modifications to extend duration and reduce absorption variability:

- Insulin glargine (eg, IGlar U100, Lantus), introduced in 2000, was modified to provide an increased isoelectric point via arginine residues, reducing solubility at physiological pH and leading to slower release (~12-15 hours).[12]
- Insulin detemir (IDet U100, Levemir), introduced in 2004, employed fatty acid modification (myristoyl group, 14-carbon) for enhanced albumin binding, extending duration to approximately 24 hours.[13]
- Insulin degludec (Tresiba U100/U200), introduced in 2015, has a hexadecanedioic acid fatty chain linked via a γ-glutamyl spacer to promote hexamer formation, allowing a duration of up to 42 hours.[14]

Each of these innovations improved stability, absorption variability,

KEY POINTS

- Once-weekly basal insulin formulations, insulin icodec and insulin efsitora alfa, have been demonstrated to provide glycemic control comparable to that with daily basal insulin in patients with type 1 diabetes mellitus (T1DM), but both are associated with a higher risk of hypoglycemia, particularly during the titration period.
- Insulin icodec has prolonged duration of action due to albumin binding and reduced insulin receptor affinity, while insulin efsitora alfa utilizes Fc-fusion technology and neonatal Fc receptor recycling that extend its half-life and enable weekly dosing.
- Although an application for marketing approval of insulin icodec was recently rejected by the US Food and Drug Administration due to safety and manufacturing concerns, ongoing research and regulatory adjustments may address these issues and shape the future role of once-weekly basal insulin in T1DM management.

Table 1. Key Differences in Mechanisms of Action of Insulin Icodec and Insulin Efsitora Alfa

Feature	Insulin icodec	Insulin efsitora alfa
Mechanism of prolonged action	Albumin binding and reduced receptor affinity	FcRn recycling system
Structural modifications	20-carbon fatty acid; 3 amino acid changes	Multiple amino acid changes; IgG2 Fc fusion
Half-life	~196 hours	~120 hours
Primary clearance pathway	Slow dissociation from albumin	FcRn-mediated recycling

Abbreviations: IgG2, immunoglobulin G2; FcRn, neonatal Fc receptor.

and hypoglycemia risk, but daily injections were still required. Icodec and efsitora, by contrast, extend the half-life beyond 100 hours, making weekly dosing possible.

Clinical developments of once-weekly insulins for the treatment of T1DM

Insulin Icodec: ONWARDS-6 Trial. The ONWARDS clinical development program has evaluated the efficacy and safety of once-weekly insulin icodec across several trials. While ONWARDS trials 1 through 5 primarily focused on type 2 diabetes mellitus (T2DM), ONWARDS-6 was the first phase 3 trial to investigate once-weekly insulin icodec in individuals with T1DM and was conducted across 99 sites in 12 countries.[4]

Patient selection. Eligible participants had a confirmed diagnosis of T1DM for at least 1 year before screening and were treated with a basal-bolus insulin regimen. Inclusion criteria required participants to have a glycated hemoglobin (HbA_{1c}) concentration below 10% at screening. Key exclusion criteria included recent myocardial infarction (MI), stroke, hospitalization for angina or transient ischemic attack (TIA) within 180 days before screening, planned revascularization, significant renal or liver impairment, hypoglycemia unawareness, and recurrent severe hypoglycemic episodes in the past year.[4]

Intervention. Participants were randomized (1:1) to receive either once-weekly icodec or once-daily degludec, both in combination with multiple daily injections of insulin aspart.[4] The dosing strategy for insulin icodec employed a novel approach (Table 2):

- The initial injection was calculated as the pretrial daily basal insulin dose multiplied by 7, with an additional one-time dose adjustment based on the HbA_{1c} value at screening. Participants with an HbA_{1c} of <8.0% received an extra 50%, while those with an HbA1c of ≥8.0% received an extra 100%.
- For participants previously treated with glargine U300 or twice-daily basal insulin, a 50% additional dose was applied regardless of the screening HbA_{1c}.
- The second injection was calculated as the pretrial basal insulin dose multiplied by 7, without additional adjustments.
- Subsequent doses were titrated weekly according to a prespecified algorithm to achieve a prebreakfast self-measured blood glucose target of 80-130 mg/dL (4.4-7.2 mmol/L).

Once-daily degludec was administered at any time of day, preferably at the same time each day. Dose adjustments were made weekly according to the same titration algorithm. Bolus insulin (aspart) was administered subcutaneously with meals, with initial doses matched unit-to-unit from pretrial insulin regimens. Dose adjustments for insulin aspart were permitted weekly during the first 8 weeks of treatment for safety reasons and could be based on self-monitored blood glucose or carbohydrate counting, depending on investigator discretion.[4]

Outcome measures. The trial's primary outcome was the reduction in HbA_{1c} from baseline to week 26. This was a noninferiority study. Secondary efficacy outcomes included changes in HbA_{1c} and fasting glucose from baseline to week 52, the proportion of time spent within the target glucose range (TIR), and patient-reported satisfaction on the Diabetes Treatment Satisfaction Questionnaire (DTSQ). The DTSQ evaluates perceived treatment satisfaction, frequency of hyper- and hypoglycemia, and overall convenience and flexibility using a 6-point Likert scale across multiple domains. Glucose metrics, including TIR and time below/above range, were assessed using continuous glucose monitoring (CGM), which provided detailed insight into glycemic variability and control. Safety outcomes assessed shifts in body weight, total insulin usage, and time spent in hypo- and hyperglycemic ranges.[4]

Results. The ONWARDS-6 trial enrolled 582 participants with type 1 diabetes who were randomly assigned to receive once-weekly insulin icodec (n = 290) or once-daily insulin degludec (n = 292). In terms of glycemic control, both groups achieved substantial reductions in HbA_{1c} by week 26. Participants receiving icodec experienced a mean decrease in HbA_{1c} ranging from 7.59% to 7.15%, while those receiving degludec saw a mean reduction ranging from 7.63% to 7.10%. The estimated treatment difference (ETD) was 0.05% (95% CI, −0.13 to 0.23),

Table 2. Comparison of Insulin Icodec and Insulin Efsitora Alfa Dosing in Clinical Trials

Dosing parameter	Insulin icodec (700 units/mL)[4]	Insulin efsitora alfa (500 units/mL)[3]
Initial dose	Pretrial daily basal insulin dose × 7: • +50% if HbA_{1c} < 8% or if previously on glargine U300 or twice-daily basal insulin • +100% if HbA_{1c} ≥ 8%	Pretrial daily basal insulin dose × 7 (rounded to nearest 10) × 3
Second dose	Pretrial daily basal insulin dose × 7	Pretrial daily basal insulin dose × 7
Weekly titration	Based on lowest self-measured glucose: • If <80 mg/dL, decrease by 20 units • If 80-130 mg/dL, no change • If >130 mg/dL, increase by 20 units	Based on average of 3 most recent fasting glucose readings[a]: • For patients taking <100units/week: o If <80 mg/dL, decrease to previous lower dose o If 80-120 mg/dL, no change o If 121-150 mg/dL, increase by 5 units o If 151-180 mg/dL, increase by 10 units o If >180 mg/dL, increase by 20 units • For patients taking >100 units/week o If <80 mg/dL, decrease to previous lower dose o If 80-120 mg/dL, no change o If 121-150 mg/dL, increase by 10 units o If 151-180 mg/dL, increase by 20 units o If >180 mg/dL, increase by 30 units

Abbreviation: HbA_{1c}, glycated hemoglobin.
[a]In the event of confirmed severe hypoglycemia, decrease dose by 20-40 units as clinically indicated.

confirming the noninferiority of icodec to degludec ($P = 0.0065$).[4]

Despite comparable HbA_{1c} reductions, the icodec group had significantly higher rates of hypoglycemia. Rates of clinically significant or severe hypoglycemia by week 26 were 19.93 events per patient-year for icodec versus 10.37 for degludec (rate ratio, 1.89 [95% CI, 1.54-2.33], $P < 0.0001$).[4] By week 52, these rates were 17.00 events per patient-year for icodec compared to 9.16 for degludec (rate ratio, 1.80 [95% CI, 1.48-2.18], $P < 0.0001$).[4] An extended analysis over the full 57-week study period, which included a 5-week follow-up phase, confirmed that hypoglycemia rates remained significantly higher with icodec.[4] Nocturnal hypoglycemia was also significantly more frequent in the icodec group at both timepoints. Importantly, most severe hypoglycemic episodes occurred during the first 12 weeks of treatment; 33 of the total of 47 severe events were reported by one participant. This highlights the need for potential adjustments in dosing algorithms or monitoring protocols to enhance safety.[4]

Patient-reported outcomes, measured via the DTSQ, showed improvements in treatment satisfaction for both groups. Interestingly, satisfaction scores were statistically significantly lower for icodec than for degludec. By week 26, the mean DTSQ score increased by 1.97 points for icodec and by 3.06 points for degludec (ETD, −1.09 [95% CI, −1.85 to −0.34], $P = 0.0044$). Similar findings persisted at week 52, with participants in the degludec group reporting greater satisfaction.[4]

Insulin efsitora alfa: QWINT-5 trial. The QWINT clinical development program evaluated once-weekly efsitora compared with once-daily insulin across a range of populations. QWINT trials 1 through 4 primarily looked at type 2 diabetes. QWINT-5 was a phase 3 randomized study conducted at 82 centers across 6 countries.[3]

Patient selection. Participants included in the trial had a diagnosis of T1DM treated with a basal-bolus insulin regimen for at least 90 days prior to screening. Exclusion criteria included a history of more than one episode of severe hypoglycemia within the 6 months before screening or a history of hypoglycemia unawareness.[3]

Intervention. Participants were randomly assigned in a 1:1 ratio to receive either once-weekly insulin efsitora alfa or once-daily insulin degludec. All participants transitioned to insulin lispro as their bolus insulin via unit-for-unit conversion from their prestudy bolus insulin regimen. For participants randomized to insulin efsitora, the following dosing strategy (also summarized in Table 2) was utilized:

- The initial dose involved a one-time loading dose, calculated as the participant's usual daily basal insulin dose (in units) multiplied by 7, rounded to the nearest 10, and then multiplied by 3. This loading dose was designed to rapidly achieve therapeutic insulin concentrations.

Table 3. Hypoglycemia Rates Reported in Clinical Trials of Insulin Icodec and Insulin Efsitora Alfa[3,4]

Hypoglycemia type	Icodec vs degludec, rate ratio (95% CI)	Efsitora vs degludec, rate ratio (95% CI)
Overall hypoglycemia		
Level 2[a]	1.79 (1.48-2.48); $P < 0.0001$	Not reported
Level 3[b]	1.88 (0.48-7.36); $P = 0.37$	3.44 (1.64-7.19); $P < 0.001$
Combined level 2 and 3	1.80 (1.48-2.18); $P < 0.0001$	1.21 (1.04-1.41); $P = 0.016$
Nocturnal hypoglycemia		
Level 2	1.88 (1.43-2.47); $P < 0.0001$	Not reported
Level 3	1.62 (0.22-11.86); $P = 0.63$	Not reported
Combined level 2 and 3	1.89 (1.44-2.48); $P < 0.0001$	1.02 (0.79-1.31); $P = 0.90$

[a]Level 2 hypoglycemia was defined as a blood glucose concentration <54 mg/dL.
[b]Level 3 hypoglycemia refers to a severe event characterized by altered mental or physical status requiring assistance for recovery.

- The second injection (administered in the second week) was calculated as the participant's usual daily basal insulin dose multiplied by 7 (rounded to the nearest 10). For instance, a participant requiring 24 units of daily basal insulin would receive a weekly insulin efsitora dose of 170 units (24 × 7) and an initial loading dose of 510 units (170 × 3).
- Subsequent doses were based on fasting glucose. For participants with baseline fasting blood glucose levels above 140 mg/dL, the protocol recommended an incremental increase to the daily basal insulin dose before determining the insulin efsitora starting dose to mitigate transient hyperglycemia while the drug reached steady-state levels. Specifically, fasting blood glucose levels between 141 and 160 mg/dL warranted a 10% to 20% increase, while levels exceeding 160 mg/dL required a 20% to 30% increase.

Participants randomized to degludec received a starting dose equivalent to their usual prestudy basal insulin dose. For those previously on insulin glargine 300 units/mL, the initial insulin degludec or insulin efsitora dose was reduced by 20% to account for differences in potency.[3]

Dosing adjustments for both basal insulins were conducted weekly through week 12 and then at least every 4 weeks or more frequently as clinically indicated. Adjustments followed a protocol algorithm based on the median of the 3 most recent fasting blood glucose values from self-monitoring in the previous week, the occurrence and severity of hypoglycemia, and investigator discretion. The target fasting blood glucose range was 80 to 120 mg/dL (4.4-6.7 mmol/L). Decreases to the basal insulin dose could be made at any time in response to hypoglycemia.[3]

Outcome measures. The primary outcome of the QWINT-5 trial, designed to assess the noninferiority of insulin efsitora relative to insulin degludec, was the reduction in HbA_{1c} from baseline to week 26. Key secondary efficacy endpoints included changes in HbA_{1c} from baseline to week 52, fasting blood glucose, and time in the target glucose range (70-180 mg/dL) as measured by CGM, and changes in the Diabetes Treatment Satisfaction Questionnaire-Change10 (DTSQ-Change10) score from baseline to weeks 26 and 52. Safety endpoints included time below the glucose range (<54 mg/dL), time above the glucose range (>180 mg/dL) as measured by CGM, and rates of clinically significant nocturnal and severe hypoglycemia.[3]

Results. Results for the primary endpoint, the reduction in HbA_{1c} from baseline to week 26, demonstrated the noninferiority of insulin efsitora to insulin degludec. The mean HbA_{1c} level decreased from 7.88% to 7.41% with efsitora and from 7.94% to 7.36% with degludec. The ETD was 0.052% (95% CI, –0.077% to 0.181%; $P = 0.43$), confirming noninferiority but not superiority. At week 52, similar trends were observed, with both treatments achieving comparable glycemic control.

Participants receiving insulin efsitora had higher rates of level 2 or level 3 hypoglycemic events when compared to those receiving degludec. From baseline to week 26, the event rate for combined level 2 or level 3 hypoglycemia was 17.19 events per patient-year of exposure (PYE) with insulin efsitora versus 14.06 events per PYE with insulin degludec (estimated rate ratio, 1.22; 95% CI, 1.04-1.43; $P = 0.013$).[3] A similar trend persisted through week 52. Severe hypoglycemia (level 3) was also more frequent with insulin efsitora, with 44 events reported among 35 participants (10%), compared to 13 reported events in 11 participants (3%) receiving insulin degludec (see Table 3). Most severe hypoglycemic episodes with use of insulin efsitora occurred during the initial 12 weeks, coinciding with the titration period.

Patient satisfaction, measured by the Diabetes Treatment Satisfaction

Questionnaire-Change (DTSQ-Change), showed statistically significant improvement for both groups. At week 26, the mean DTSQ-Change score increased by 14.4 points with insulin efsitora compared to 13.2 points with insulin degludec ($P = 0.0081$).[3] This trend persisted through week 52, suggesting that participants valued the convenience of the once-weekly regimen despite the higher rates of hypoglycemia.

Patient considerations

Adherence and satisfaction. Managing T1DM requires lifelong adherence to insulin therapy, yet adherence to nonpump insulin regimens remains a challenge. Studies indicate that poor adherence contributes to suboptimal glycemic control, leading to an increased risk of complications. A retrospective study in Qatar found that only 40.9% of adolescents with T1DM met adherence criteria, with nonadherent patients having a significantly higher mean HbA_{1c} level than adherent patients (9.7% vs 9.0%, $P = 0.002$).[15] Nonadherence was identified as an independent predictor of poor glycemic control, reducing the likelihood of achieving an HbA_{1c} level of <7% by 78%. This highlights the need for interventions aimed at improving adherence among individuals with T1DM.[15] Several factors contribute to nonadherence in insulin therapy, including the following[15]:

- Lack of education or understanding of insulin regimens and glucose management
- Time constraints and difficulty integrating multiple daily injections into busy schedules
- Inconvenience of injections in public or workplace settings, leading to missed doses
- Emotional and psychological burden, including injection fatigue and distress

Once-weekly basal insulin formulations have the potential to address some of these barriers by reducing the number of injections required for glycemic control. Theoretically, this could improve adherence, simplify insulin regimens, and enhance patients' quality of life. However, the impact of these therapies on patient-reported outcomes remains inconsistent, as evidenced by the ONWARDS-6 and QWINT-5 trials.[3,4]

The ONWARDS-6 trial evaluating insulin icodec found that while patient satisfaction scores improved in both groups, the mean increase was significantly lower for insulin icodec than for insulin degludec (1.97 vs 3.06, $P = 0.0044$).[4] Subscale analysis of the DTSQ revealed that participants in the icodec group provided lower ratings in the domain of treatment flexibility. While the DTSQ does not define "flexibility" explicitly, this score may reflect participants' perceptions of their ability to adjust basal insulin dosing or respond to day-to-day changes in routine.[4]

In contrast, the QWINT-5 trial reported higher overall patient satisfaction scores for efsitora versus degludec (14.4 vs 13.2, $P = 0.0081$), suggesting a more favorable reception among participants in that study.[3] The reasons for this discrepancy remain unclear but may relate to differences in study populations, trial design, or participant familiarity with weekly therapeutic regimens.

Overall, while once-weekly insulin therapy has the potential to improve adherence, the conflicting patient satisfaction results highlight the importance of individualized treatment approaches. Further research is needed to identify patient populations best suited for weekly basal insulin and to refine strategies that support a smooth transition from daily regimens.

Cost implications. Although once-weekly basal insulins like icodec and efsitora are not yet approved in the United States, they have been introduced in other countries. Understanding the cost implications of these agents compared to traditional daily basal insulins is crucial, as cost plays a significant role in treatment accessibility and adherence.

In Canada, insulin icodec (marketed as Awiqli) has been approved and is priced similarly to insulin degludec, with annual costs ranging from $1,148 to $1,956, depending on the dosage.[16] In China, a cost-utility analysis suggested that insulin icodec could be a cost-effective alternative to insulin degludec if its annual cost ranged between $597.66 and $736.34 for patients with T2DM.[17] In Italy, an economic evaluation from the perspective of the Italian National Healthcare System indicates that even if insulin icodec were priced 25% higher than insulin degludec, the reduced injection frequency and potential improvements in adherence could lead to overall cost savings and enhanced quality of life.[18]

These findings suggest that while the upfront cost of once-weekly insulins may be slightly higher or comparable to that of daily basal insulins, the potential benefits—including improved adherence, reduced healthcare utilization, and fewer missed doses—could offset the cost over time. However, insulin pricing varies significantly across countries due to factors such as healthcare policies, insurance coverage, and market dynamics.

In the United States, where insulin prices are notably higher than in many other countries, the economic impact of once-weekly basal insulins remains uncertain. A recent analysis comparing insulin prices found that the average gross manufacturer price for a standard unit of insulin in the US was more than 10 times higher than in 32 foreign countries.[19] Given this disparity, the introduction of a once-weekly insulin may have different cost implications depending on pricing strategies, insurance coverage, and patient assistance programs.

Ultimately, while once-weekly basal insulins offer a promising advancement in diabetes management, their adoption and accessibility will depend heavily on cost considerations. Further real-world studies are needed to determine their cost-effectiveness

relative to daily basal insulins and assess their potential financial impact on healthcare systems and patients.

Considerations for vulnerable populations. Additionally, certain populations may face unique challenges with once-weekly basal insulin. For example, patients with low serum albumin levels—common in chronic illness or malnutrition—may experience altered pharmacokinetics with icodec, which relies on albumin binding.[2] Similarly, individuals with food insecurity or irregular meal patterns may be at increased risk for hypoglycemia due to the prolonged duration of weekly insulin and the inability to easily adjust dosing in response to missed meals.[20]

Regulatory landscape and future directions

In July 2024, Novo Nordisk's application for marketing approval of once-weekly insulin icodec was declined by FDA. The agency issued a complete response letter (CRL) citing concerns related to the manufacturing process as well as the clinical use of icodec in patients with T1DM—particularly the elevated risk of hypoglycemia observed during clinical trials. In response, Novo Nordisk has expressed its commitment to resolving these issues and is actively working with FDA to identify the necessary steps to complete the review process. Despite this regulatory setback, Novo Nordisk continues to advance its once-weekly insulin program.[21]

In contrast, Eli Lilly's once-weekly insulin, efsitora alfa, has been demonstrated to have efficacy comparable to that of daily insulin injections in managing blood glucose levels in both T1DM and T2DM. However, clinical trials have reported a higher frequency of hypoglycemic events during the initial 12 weeks of treatment with efsitora, particularly among patients with T1DM.[3] This raises questions about its approval prospects, as FDA has previously expressed concerns over hypoglycemia risks associated with once-weekly insulin formulations.

Given these considerations, it remains uncertain whether efsitora will address the FDA concerns that led to the rejection of icodec. The increased incidence of hypoglycemia observed with efsitora may pose challenges for its approval in the treatment of T1DM.

Although once-weekly insulins have been approved in some international markets, real-world outcomes data are currently limited and may not yet be generalizable to US populations. As global use expands, postmarketing surveillance and real-world effectiveness studies will be essential to better understand long-term safety and glycemic outcomes across diverse care settings.

Conclusion

Once-weekly basal insulin formulations represent a promising advancement in the management of T1DM by potentially improving adherence and reducing the burden of daily injections. Clinical trials, including ONWARDS-6 and QWINT-5, have demonstrated that these agents achieve glycemic control comparable to daily basal insulin; however, the increased risk of hypoglycemia—particularly during the early titration phase—remains a significant concern. While patient satisfaction data are mixed, with insulin efsitora a a more favorable response than icodec, the variability highlights the need for individualized patient selection and optimized dosing strategies. Cost-effectiveness analyses from international markets suggest that once-weekly insulins could be priced similarly to daily options, though US pricing remains uncertain. Despite insulin icodec's FDA rejection due to manufacturing concerns and safety issues, insulin efsitora's regulatory path remains unclear, as it shares similar challenges. Notably, current trials are limited by relatively short follow-up durations, narrow study populations, and a lack of real-world data. Moving forward, further research is needed to refine titration protocols, identify the ideal patient population, and address safety concerns to enhance the viability of once-weekly basal insulin in T1DM management.

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