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A Comparative Assessment of Insulin Efsitora Alfa and Insulin Icodec in Diabetes Mellitus Management: A Scooping Review

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KEYWORDS

Diabetes Mellitus; Efficacy; Hypoglycemia; Insulin Efsitora Alfa; Insulin Icodec; Safety

ABSTRACT

Diabetes Mellitus management continues to evolve with innovations in insulin therapy aimed at improving efficacy and patient comfort. This study aims to compare the efficacy and safety of Insulin Efsitora Alfa and Insulin Icodec in the management of *Diabetes Mellitus*. This scoping review analyzed articles published between August 2020 and August 2025 from PubMed, ScienceDirect, and other sources. Inclusion criteria included English-language observational studies addressing the efficacy and safety of both insulins in *DM*. Ten articles were selected after a rigorous screening process. Both insulins demonstrated non-inferior efficacy in lowering HbA1c compared to daily basal insulin, with pharmacokinetic/pharmacodynamic profiles favoring once-weekly dosing. General tolerability was good, and Time in Range (TIR) was comparable. However, Insulin Icodec was associated with a higher incidence of hypoglycemia, especially in type 1 diabetes, compared to Insulin Efsitora Alfa, which showed similar hypoglycemia rates to daily insulin. Patient satisfaction with Icodec was higher in type 2 diabetes but lower in type 1. Both insulins offer the potential to improve patient adherence. Insulin Efsitora Alfa may be more suitable for patients prone to hypoglycemia. The increased risk of hypoglycemia with Insulin Icodec requires careful clinical consideration and dose titration. Further head-to-head comparison studies are needed to guide optimal therapy.

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INTRODUCTION

The global health system and public health are greatly impacted by *diabetes mellitus*, a chronic illness whose incidence is steadily rising. An efficient and secure method is necessary for managing diabetes, especially when using insulin, a crucial part of diabetes treatment (American Diabetes Association, 2025). Insulin Efsitora Alfa and Insulin Icodec are two novel forms of insulin that have been developed as substitutes for conventional insulin therapy in recent years. With doses administered just once a week, both of these insulins offer the advantage of less frequent injections, which can enhance patient compliance and lessen the burden of therapy (National Library of Medicine, 2025).

The efficacy of Efsitora Alfa insulin in regulating blood glucose levels has been demonstrated; the results suggest that it is on par with daily basal insulins like insulin degludec. According to studies, there have been no reports of severe hypoglycemia, and side effects are generally mild and unrelated to the medication. Because of this, Efsitora Alfa is a desirable choice for people who need more adaptable diabetic care (Dutta et al., 2025). In addition, compared to other insulins, Icodec insulin exhibits a favorable safety profile, with no elevated

risk of allergic reactions. Icodec insulin maintains a good time-in-range (TIR), similar to daily basal insulin, and even exhibits a longer duration in the desired glucose range than insulin glargine or degludec, according to analyses of Continuous Glucose Monitoring (CGM) data (Bajaj et al., 2024; Mikhail, 2024).

Comparing Insulin Efsitora Alfa and Insulin Icodec in terms of efficacy and safety is crucial for determining the optimal therapy option for *diabetes* patients. A better understanding of these two insulins is expected to improve patients' quality of life and overall *diabetes* management outcomes. The aim of this study was to conduct a comparative assessment of the effectiveness and safety of Insulin Efsitora Alfa and Insulin Icodec in the management of *diabetes mellitus*. Further research and in-depth comparative analyses will provide clearer insights into the benefits and risks of each therapy, thus aiding better clinical decision-making.

The findings from this comparative assessment are anticipated to provide significant benefits for various stakeholders. For clinicians, this review offers a synthesized evidence base to guide personalized treatment decisions, helping to select the most suitable once-weekly insulin based on a patient's individual risk profile, particularly concerning hypoglycemia. For patients, this research highlights therapeutic options that can reduce injection frequency, potentially improving treatment adherence and quality of life. For healthcare policymakers and researchers, this scoping review identifies key similarities, differences, and evidence gaps, thereby informing future health technology assessments and guiding the direction of subsequent comparative effectiveness research.

METHOD

This research uses a scoping review as the main method to review and map the available evidence on the topic studied. The scoping review was selected to identify key concepts, review relevant literature, and identify gaps in research related to the comparison of the efficacy and safety of Insulin Efsitora Alfa and Insulin Icodec in the management of *Diabetes Mellitus*. This method is suitable for relatively new and evolving topics, as it allows researchers to filter, evaluate, and synthesize findings from various studies without conducting an in-depth critical assessment of methodological quality, as required in systematic reviews.

The first steps in the data collection process involved processing written materials by reading and recording them and gathering library data as part of a literature study. Topics covered in published articles or associated publications served as data sources. The scoping review is the method employed in this research.

The questions in the articles were arranged according to the PICO (Population, Intervention, Comparison, Outcome) framework. *DM* patients are represented by P; Insulin Efsitora Alfa and Insulin Icodec therapy are represented by I; the comparison of the safety and effectiveness of Insulin Efsitora Alfa and Insulin Icodec is represented by C; and *Diabetes Mellitus* management is represented by O. The literature search was carried out in August 2025. The knowledge obtained was secondary, derived from earlier research findings rather than direct observation. Secondary data sources included articles from international publications

with predefined themes. We searched for English-language literature using three databases: PubMed, ScienceDirect, and additional sources. The keywords used were “comparing” AND “efficacy” AND “safety” AND “Insulin Efsitora Alfa” AND “Insulin Icodec” AND “*Diabetes Mellitus* management.”

The inclusion criteria for the literature search were: (1) articles discussing the effects of Efsitora Alfa insulin therapy and Icodec insulin therapy on the management of *Diabetes Mellitus*; (2) articles comparing the efficacy and safety of Efsitora Alfa insulin therapy and Icodec insulin therapy on the management of *Diabetes Mellitus*; (3) English-language publications; (4) articles published between August 2020 and August 2025; (5) research articles with observational study designs; (6) articles with abstracts; and (7) articles with full text available. Meanwhile, studies that were scoping reviews, literature reviews, or meta-analyses met the exclusion criteria.

In the first step of the article search (identification), 302 publications were located using three data sources: PubMed, ScienceDirect, and other sources. Of these, 152 were from ScienceDirect, 125 were from PubMed, and 25 were from other sources. After removing 10 duplicates, 292 items remained. The second step, known as "screening," entailed reviewing article titles to verify the presence of abstracts and assessing whether the abstract content related to the literature review’s topic. Articles not meeting the criteria were removed. A total of 231 articles were excluded, leaving 61 articles with titles that met the requirements. As part of the "eligibility" process, articles from scoping reviews, systematic reviews, and meta-analyses were excluded. Additionally, free full-text articles addressing the safety and effectiveness of Icodec and Efsitora Alfa insulin therapy in the treatment of *diabetes mellitus*, published within the previous five years (August 2020–August 2025), were reviewed. After removing 40 articles, 21 remained. The final phase, referred to as the "inclusion" step, involved selecting the number of papers that best fit the inclusion and exclusion criteria and aligned with the objectives of this scoping study. Ten articles satisfied all standards, while the remaining eleven were excluded. The flowchart below (Figure 1) details the outcomes of the article selection procedure.

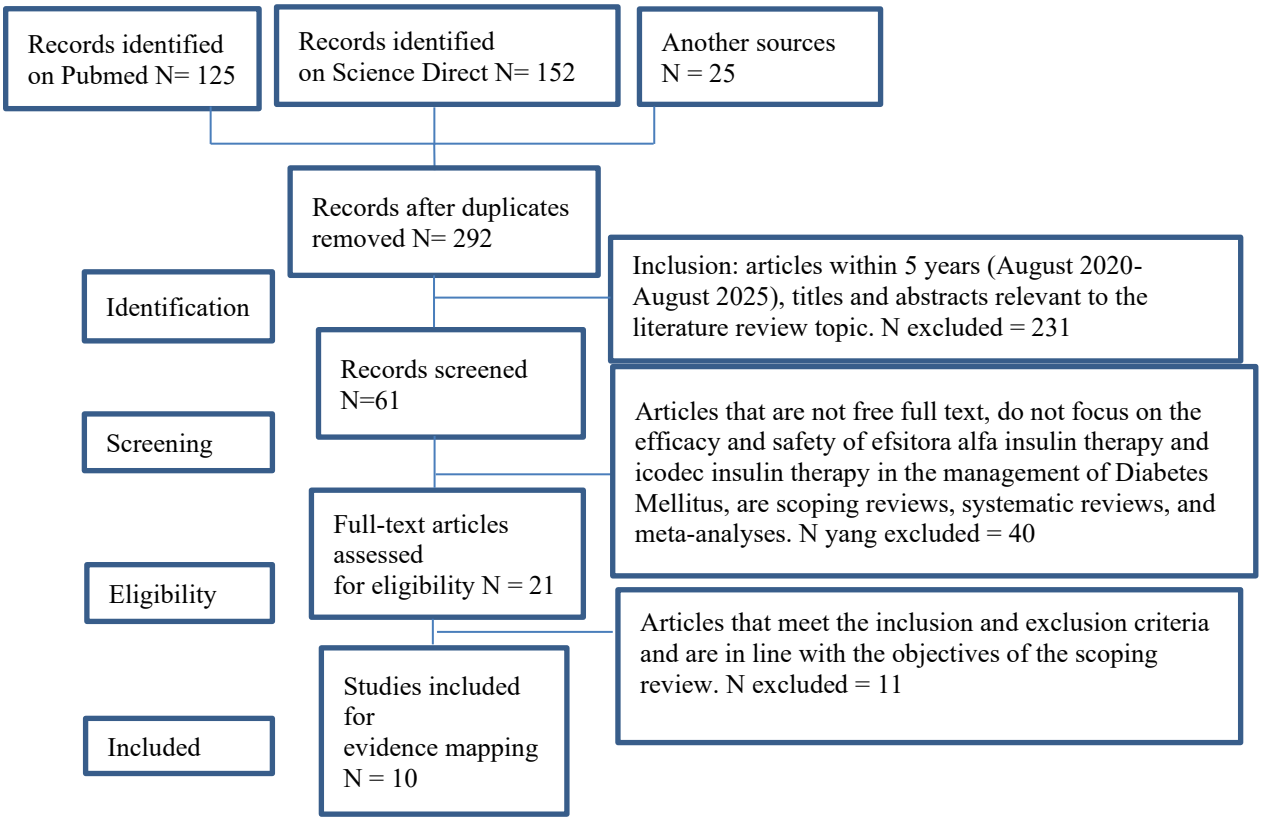

Figure 1. PRISMA-based flow diagram

Source: Developed by the author based on the PRISMA method

RESULTS AND DISCUSSION

Table 1. Comparison of the Efficacy and Safety of Insulin Efsitora Alfa and Insulin Icodec in the Management of Diabetes Mellitus

No	Author, Title	Aim	Results	Conclusion
1	Blevins et al. (2025) Once-weekly insulin efsitora alfa versus once-daily insulin glargine U100 in adults with type 2 diabetes treated with basal and prandial insulin (QWINT-4): a phase 3, randomized, non-inferiority trial	To evaluate the safety and effectiveness of once-daily insulin glargine U100 with once-weekly insulin efsitora alfa (efsitora) in individuals with type 2 diabetes receiving basal and prandial insulin.	• In terms of the change in HbA1c from baseline to week 26, Efsitora showed no inferiority to glargine U100. The efsitora group experienced a mean change in HbA1c of -1.01% from baseline to week 26, while the glargine U100 group experienced a mean decrease of -1.00%. • Glargine U100 and efsitora had comparable rates of nocturnal level 2 or level 3 (severe) hypoglycemia and overall hypoglycemia. • The two groups experienced side effects at comparable rates. • In comparison to glargine U100, the efsitora group's weekly basal insulin dosage and weekly total insulin dose were considerably lower. • When using efsitora, the average daily prandial insulin dosage was considerably reduced.	Efsitora demonstrated non-inferior HbA1c reductions and similar rates of clinically significant or severe hypoglycemia compared to glargine U100. This demonstrates that efsitora is a well-tolerated and effective once-weekly alternative to daily basal insulin, with reduced injection frequency.

2	Nasu et al. (2025) Pharmacokinetic and Pharmacodynamic Properties of Once-Weekly Insulin Efsitora Alfa in Japanese Patients with Type 2 Diabetes	To describe the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of insulin efsitora alfa (efsitora) in Japanese patients with type 2 diabetes, as well as to evaluate the medication's safety and tolerability.	• Following the last dose, the PK profile revealed a low peak-to-trough ratio (1.13), along with a lengthy half-life (15–16 days). • From baseline to day 15 (single-dose study), mean fasting glucose levels were lowered by all efsitora dosages (5, 10, and 20 mg). • Following the changeover from insulin degludec, no notable alterations were noted (multiple dosage trial). • Every side effect that happened during therapy was minor and had nothing to do with the medication under study. • There were no reports of severe hypoglycemic episodes.	Efsitora was well tolerated, and the PK/PD profile was consistent with findings in previous global studies, supporting the participation of Japanese patients in the phase 3 study.
3	Heise et al. (2024) Frequency and Severity of Hypoglycemia Under Conditions of Increased Hypoglycemic Risk with Insulin Efsitora Alfa Versus Insulin Glargine Treatment in Participants with Type 2 Diabetes	To evaluate efsitora's risk of hypoglycemia in comparison to glargine in provocation conditions that are representative of real-world scenarios (double dosage of study insulin, prolonged fasting, and prolonged fasting with exercise).	• No instances of severe hypoglycemia were noted. Level 1 hypoglycemia episodes (≥54 to <70 mg/dL) accounted for the majority of cases. • There was no discernible difference in the incidence of level 1 hypoglycemia between efsitora and glargine when prolonged fasting, prolonged fasting combined with exercise, and multiple dosing were present. • Neither medication nor any provocation was associated with level 2 hypoglycemia (<54 mg/dL). • For both therapies, the mean glucose nadir and hypoglycemia duration were comparable.	When compared to daily glargine during the provocation period, once-weekly Efsitora did not increase the occurrence, duration, or severity of hypoglycemia in patients with type 2 diabetes.
4	Heise et al. (2022) Pharmacokinetic and pharmacodynamic properties of the novel basal insulin Fc (insulin efsitora alfa), an insulin fusion protein in development for once-weekly dosing for the treatment of patients with diabetes	To evaluate basal insulin Fc (BIF; LY3209590), a fusion protein that combines a new single-chain insulin variation with the Fc domain of human IgG2, after once-weekly single-dose and multiple-dose administration of BIF, in terms of safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD).	• No severe hypoglycemia was noted; BIF has a PK half-life of roughly 17 days, meaning that it reduces fasting blood glucose in a dose-dependent manner for at least 5 days. • Following the final dosage at week 6 (steady state), BIF displayed a low peak-to-trough ratio of 1.14. • The BIF seven-point glucose profile held steady over the course of six weeks, resembling insulin glargine. • BIF hypoglycemia events are comparable to insulin glargine in terms of both length and rate.	BIF was well tolerated, and throughout a one-week treatment interval, its PK/PD profile permitted once-weekly dosage with little exposure fluctuation. According to these results, BIF may be developed further as a weekly basal insulin for diabetics.

5	Bajaj et al. (2024) Continuous Glucose Monitoring-Based Metrics and Hypoglycemia Duration in Insulin-Experienced Individuals with Long-standing Type 2 Diabetes Switched From a Daily Basal Insulin to Once-Weekly Insulin Icodec: Post Hoc Analysis of ONWARDS 2 and ONWARDS 4	To evaluate the duration of hypoglycemia and Continuous Glucose Monitoring (CGM)-based metrics in insulin-experienced people with long-standing type 2 diabetes using once-weekly insulin icodec as opposed to a once-daily basal insulin analogue.	• Across all time periods, there were no statistically significant changes in TIR, TAR, or TBR (<3.0 mmol/L) between comparators (glargine U100 in ONWARDS 4; degludec in ONWARDS 2). • TBR stayed within the globally advised ranges of <4% and <1%, respectively (<3.9 mmol/L and <3.0 mmol/L). • Across time periods and treatment groups, the median length of CGM-derived hypoglycemia episodes (<3.9 mmol/L) was comparable (median duration ≤40 minutes). • Level 2 hypoglycemia (<3.0 mmol/L) was not present during most CGM-derived hypoglycemia events.	CGM-based measures (TIR, TAR) and CGM-derived hypoglycemia duration (<3.9 mmol/L) were similar for icodec and a once-daily basal insulin analogue in insulin-experienced individuals with chronic type 2 diabetes. TBR stayed within the suggested range. These results provide credence to the effectiveness and safety of icodec in people with type 2 diabetes who have previously used insulin.
6	Kjeldsen et al. (2021) Molecular Engineering of Insulin Icodec, the First Acylated Insulin Analog for Once-Weekly Administration in Humans	Describes the molecular engineering of insulin icodec to obtain a plasma half-life of 196 hours in humans, suitable for once-weekly subcutaneous delivery, and offers structure-activity relationship research leading to insulin icodec.	In humans, insulin icodec has a 196-hour plasma half-life. In individuals with type 2 diabetes, once-weekly insulin icodec produced glycemic control that was both safe and effective, on par with once-daily insulin glargine, according to a phase 2 clinical trial.	With a half-life of 60 hours in dogs and 196 hours in humans, insulin icodec is an extremely long-acting insulin analog that exerts strong glucose-lowering effects in rats.
7	Nishimura et al. (2021) Molecular and pharmacological characterization of insulin icodec: a new basal insulin analog designed for once-weekly dosing	Explains the biological, pharmacological, and molecular engineering characteristics of insulin icodec, including its in vitro characterization and clinical pharmacological assessment in people with type 2 diabetes.	The three amino acid changes (A14E, B16H, and B25H) that boost strong and reversible albumin binding and decrease insulin receptor (IR) binding affinity give insulin icodec its long half-life. Without increased mitogenicity or binding to the insulin-like growth factor-1 receptor, insulin icodec has the same biological characteristics as normal human insulin. The glucose-lowering impact is consistent throughout the week, with an average half-life of 196 hours.	A novel basal insulin with pharmacokinetic and pharmacodynamic characteristics appropriate for once-weekly dose is produced by molecular changes to icodec insulin.
8	Philis-Tsimikas et al. (2022) Rationale and design of the phase 3a development	Describes the ONWARDS phase 3a clinical development program	When compared to currently available daily basal insulin analogues, the ONWARDS program will assess the safety and effectiveness of once-weekly icodec in patients with T2D and T1D. In	Comprehensive data on the utilization of icodec in a range of groups with varying stages of diabetes development

	program (ONWARDS 1 – 6 trials) investigating once-weekly insulin icodec in diabetes	(ONWARDS 1-6) investigating once-weekly insulin icodec in diabetes, including the design and rationale for each trial.	insulin-naive T2D patients, a phase 2 research showed that once-weekly icodec lowers HbA1c with a low rate of hypoglycemia, comparable to once-daily glargine U100.	and treatment experiences will be produced by the ONWARDS 1-6 trial.
9	Russell-Jones et al. (2023) Once-weekly insulin icodec versus once-daily insulin degludec as part of a basal-bolus regimen in individuals with type 1 diabetes (ONWARDS 6): a phase 3a, randomized, open-label, treat-to-target trial	In people with type 1 diabetes, comparing the safety and effectiveness of once-daily insulin degludec versus once-weekly subcutaneous insulin icodec	When it came to lowering HbA1c at week 26, once-weekly icodec was not inferior than once-daily degludec in persons with type 1 diabetes. Nevertheless, icodec had a statistically greater rate of clinically significant or severe hypoglycemia (19.9 events per patient-year of exposure) than degludec (10.4 occurrences per patient-year of exposure). Time below 3.0 mmol/L (<54 mg/dL) was below target during weeks 48–52 and below the globally advised target threshold (<1%) during weeks 22–26.	Although it has a higher risk of hypoglycemia, once-weekly insulin icodec lowers HbA1c in T1D just as well as once-daily degludec. Consideration should be given to decreased flexibility and the possibility of elevated hypoglycemia.

10	Mikhail, (2024) Efficacy and Safety of Once-Weekly Insulin ICODEC	Reviewing the efficacy and safety of insulin icodec in patients with type 1 and type 2 diabetes.	**Efficacy:**
			• **HbA1c decrease:**
			  • In four out of the six ONWARDS trials, insulin icodec reduced HbA1c levels marginally more than once-daily insulin glargine or degludec, with a mean difference of 0.19 to 0.38 percentage points.
			  • Insulin icodec was not less effective than insulin degludec in reducing HbA1c levels in two more trials (ONWARDS 4 and 6).
			• **Time in Range (TIR):**
			  • When comparing insulin icodec to insulin glargine or degludec, analysis of continuous glucose monitoring (CGM) data revealed that the former spent more or comparable amounts of time in the range (70–180 mg/dl).
			  • Compared to insulin glargine, the ONWARDS 1 trial found that insulin icodec reduced the percentage of time spent with blood glucose levels above range (> 180 mg/dl) by about one hour.
			
			Security:
			• **Hypoglycemia:**
			  • Insulin icodec was more likely to cause level 1 hypoglycemia (BG 54–69 mg/dl) than insulin
				• Insulin icodec is a convenient once-weekly basal insulin that works similarly to or marginally better than insulin glargine or degludec. It is linked to a higher risk of hypoglycemia, particularly in people with type 1 diabetes.
				• Its lengthy duration of action and potential improper dose titration (a titration regimen of 20 units per week may be too vigorous) may be the cause of the elevated risk of hypoglycemia.

	glargine or degludec (ERR varied from 1.25 to 1.88). • In three of the six ONWARDS trials, insulin icodec significantly increased (71–89%) the incidence of combined level 2 (BG < 54 mg/dl) and level 3 (needing external assistance) hypoglycemia as compared to insulin glargine or degludec. • Compared to degludec, insulin icodec significantly increased the incidence of hypoglycemia (levels 1, 2, 3, and nocturnal) in individuals with type 1 diabetes (by about threefold at 57 weeks). • **Patient Satisfaction and Compliance:** • Compared to insulin glargine or degludec, insulin icodec improves patient satisfaction and adherence in type 2 diabetes. • Nevertheless, satisfaction ratings for insulin icodec were lower than those for degludec in people with type 1 diabetes.

Source: Data compiled and analyzed by authors from selected studies

A major advancement in the treatment of diabetes mellitus, once-weekly basal insulin has the potential to increase patient convenience and compliance. Insulin icodec and insulin efsitora alfa are two of the top contenders in this area. A once-weekly basal insulin, insulin efsitora alfa (efsitora) is a fusion protein that combines the Fc domain of human IgG2 with a unique single-chain insulin variation. Because of its low peak-to-trough ratio, this insulin, which is intended for once-weekly subcutaneous delivery, may result in more stable glucose levels (reduced glucose variability) over the course of the week (Biro & Czapar, 2025). Meanwhile, insulin icodec is a full-agonist recombinant human insulin analog that can be administered once weekly due to its extremely long half-life (196 hours) (Ingrasciotta et al., 2024).

Efsitora is now the second long-acting, once-weekly insulin analogue to be assessed in a rigorous phase 3 study and demonstrated to be equivalent to daily insulin, thanks to the new findings from QWINT. The European Medicines Agency has authorized icodec, another once-weekly insulin, for use in type 1 and type 2 diabetes (Mathieu et al., 2025). Based on the results of the trials shown in the table, this discussion will compare the safety and effectiveness of these two insulins, pointing out parallels, divergences, and other supporting data.

1. Efficacy and Safety Equations

a. Non-Inferior HbA1c Reduction:

Both insulin efsitora alfa and insulin icodec showed non-inferior efficacy in lowering HbA1c levels compared with standard daily basal insulin (glargine U100 or degludec) in patients with type 2 diabetes.

1) Efsitora Alfa: The study by Blevins et al. (2025) showed that the mean change in HbA1c from baseline to week 26 was for efsitora and for glargine U100, confirming non-inferiority (Blevins et al., 2025).
2) Icodec: The ONWARDS study showed that icodec was non-inferior to degludec in lowering HbA1c in type 1 diabetes (Russell-Jones et al., 2023) and in 2 of 6 ONWARDS trials, icodec was non-inferior to insulin degludec in lowering HbA1c levels (Mikhail, 2024). In fact, in 4 of 6 ONWARDS trials, HbA1c reductions were slightly greater with icodec than with glargine or degludec (Mikhail, 2024).

This is corroborated by another study by Rosenstock et al., which found that both insulins were equally effective at lowering HbA1c when compared to daily basal insulin. Efsitora alfa demonstrated notable A1C reductions in comparison to insulin degludec, demonstrating its strong efficacy (Biro & Czapar, 2025), whereas another trial demonstrated that insulin icodec was successful in lowering HbA1c levels over 26 to 78 weeks (Lisco et al., 2024). Compared to daily insulin, insulin efsitora alfa offered superior glucose management without raising the possibility of severe adverse effects (American Diabetes Association, 2025). Additionally, it was discovered that insulin efsitora alfa was just as effective as insulin degludec at reducing HbA1c levels in individuals with type 2 diabetes (National Library of Medicine, 2025).

Another study indicated that, when compared to a once-daily insulin regimen, BIF was non-inferior at 0.01 (95% CI -0.11 to 0.13), while Icodec was superior at -0.12 (95% CI -0.20 to -0.04) in terms of lowering HbA1c in T2DM. An alternative to the existing once-daily basal insulin regimen may be the once-weekly insulin regimen, which demonstrated greater HbA1c reduction while keeping a comparable safety profile (Richardson et al., 2025).

b. Pharmacokinetic (PK) and Pharmacodynamic (PD) Profiles that Allow Once-Weekly Dosing

Both insulins are designed for once-weekly administration with long half-lives.

1) Efsitora Alfa: Nasu et al. (2025) reported a prolonged half-life (15 to 16 days) with a low peak-to-trough ratio (1.13), supporting once-weekly dosing (Nasu et al., 2025).
2) Icodec: Kjeldsen et al. (2021) and Nishimura et al. (2021) confirmed a plasma half-life of icodec of approximately 196 hours (approximately 8 days), which allows once-weekly dosing with a uniform glucose-lowering effect throughout the week (Kjeldsen et al., 2021; Nishimura et al., 2021).
3) Development of Basal Fc Insulin (BIF; LY3209590): Heise et al.'s (2022) study of basal Fc insulin (BIF) showed that BIF has a PK half-life of approximately 17 days and is well tolerated, with a PK/PD profile that allows once-weekly dosing. The rate and duration of BIF hypoglycemia events are similar to those of insulin glargine (Heise et al., 2022). These

findings support the concept of once-weekly basal insulin in general and suggest that an insulin with a hypoglycemia safety profile comparable to daily insulin is achievable.

Additional studies from Bergenstal et al. (2025) corroborate this conclusion, stating that icodec and efsitora have lengthy half-lives in terms of their pharmacological and pharmacokinetic characteristics. They differ in their peak-to-trough ratios, which over time lead to less fluctuation in glucose levels with efsitora. With a longer and flatter exposure profile, soluble basal insulins such as insulin icodec (Novo Nordisk) and insulin efsitora alfa (basal insulin Fc [BIF]) can lower pharmacodynamic variability, possibly lower hypoglycemia, function similarly to once-daily basal insulin, make dosing easier, and enhance treatment compliance (Rosenstock et al., 2024). In a different trial, Icodec's pharmacokinetic steady state was typically reached two to three weeks into treatment. Two encouraging investigations on the pharmacological characteristics of Icodec in people with type 1 diabetes showed that, when taken once weekly, Icodec may be able to give basal insulin coverage (Eto et al., 2024; Hövelmann et al., 2024). Efsitora, on the other hand, offers pharmacokinetic characteristics that enable steady and consistent availability all week long, potentially lowering glucose variability (American Diabetes Association, 2025).

c. Good General Tolerability

In general, both insulins are well tolerated.

1) Efsitora Alfa: The Nasu et al. (2025) study reported that all adverse events were mild and unrelated to the study drug, with no severe hypoglycemia events (Nasu et al., 2025).
2) Icodec: Allergic reactions do not increase with the use of insulin icodec (Mikhail, 2024).
3) Comparable or Better Time in Range (TIR): Continuous Glucose Monitoring (CGM) data analysis showed that both insulins maintained good TIR. Bajaj et al. (2024) found that TIR, TAR, or TBR (<3.0 mmol/L) for icodec was comparable to daily basal insulin (Bajaj et al., 2024). Mikhail (2024) also noted that CGM analysis showed greater or similar time spent in the range (70-180 mg/dL) with insulin icodec compared to insulin glargine or degludec (Mikhail, 2024).

In a different study, individuals with type 2 diabetes who received efsitora and once-daily basal insulin experienced similar rates of injection site reactions, hypersensitivity events, total and severe hypoglycemia, and severe adverse events. However, efsitora was associated with a lower risk of nocturnal hypoglycemia (risk ratio 0.85 [0.74, 0.98]; P = 0.03). While the risks of hypersensitivity events and total, severe, and nocturnal hypoglycemia were similar, efsitora was associated with greater rates of injection site responses, total adverse events, and severe adverse events in people with type 1 diabetes. Similar in glycemic effectiveness to once-daily degludec, once-weekly basal insulin efsitora alfa was well tolerated (Dutta et al., 2025). Because of its tolerability and promising safety results regarding hypoglycemia, insulin icodec in particular is currently a contender to replace weekly basal insulin as the mainstay, enhancing patient adherence (Argano et al., 2024).

2. Differences in Efficacy and Safety

a. Hypoglycemia Incident

This is the most striking difference between the two insulins.

1) Efsitora Alfa: Studies have shown that rates of overall and nocturnal grade 2 or 3 (severe) hypoglycemia are similar between efsitora and glargine U100 (Blevins et al., 2025). Heise et al. (2024) further confirmed that efsitora did not increase the incidence, duration, or severity of hypoglycemia compared to daily glargine, even under provocation conditions (Heise et al., 2024).
2) Icodec: In contrast, insulin icodec is associated with an increased incidence of hypoglycemia, particularly in type 1 diabetes (Mikhail, 2024). Russell-Jones et al. (2023) reported that in type 1 diabetes, the rate of clinically significant or severe hypoglycemia was statistically higher with icodec (19.9 events per patient-year of exposure) than with degludec (10.4 events per patient-year of exposure) (Russell-Jones et al., 2023). Mikhail (2024) detailed that the incidence of grade 1 hypoglycemia was higher with icodec, and in 3 of the 6 ONWARDS trials, the incidence of grade 2 and 3 hypoglycemia combined was significantly higher (71-89%) with icodec (Mikhail, 2024). This increased risk of hypoglycemia may be due to its long duration of action and the possibility of inappropriate dose titration (Mikhail, 2024).

Insulin icodec (Novo Nordisk) and insulin efsitora alfa (basal insulin Fc [BIF], Eli Lilly and Company), two insulins meant for once-weekly delivery, have the potential to advance basal insulin replacement. Once-weekly insulin has a similar risk of hypoglycemia and provides comparable glycemic control to its once-daily equivalent, according to data from the phase 3 icodec program and phase 2 clinical investigations of efsitora and icodec (Rosenstock et al., 2024). Because of its shown efficacy, lesser hypoglycemia, and fewer injections, long-acting weekly basal insulin exhibits comparable and better glycemic efficacy than daily basal insulin in both T1DM and T2DM (Argano et al., 2024).

The incidence of combined levels 2 and 3 (moderate to severe) hypoglycemia did not rise in response to Efsitora's improvements in glycemic control. In QWINT-1, QWINT-3, and QWINT-4, the low incidence of hypoglycemia with once-weekly efsitora was similar to the incidence of hypoglycemia with the daily insulin comparison (Tsimikas et al., 2025). According to other research, in order to gain a better understanding of the risk of hypoglycemia in comparison to the currently available daily basal insulins, Phase 3 data with efsitora and practical experience with both once-weekly insulins will be required (Pieber et al., 2024).

b. Patient Satisfaction and Compliance

There are differences in patient satisfaction between the two types of diabetes. In type 2 diabetes, patient satisfaction and adherence are superior with insulin icodec compared to insulin glargine or degludec. However, in type 1 diabetes, satisfaction scores are lower with insulin icodec compared to degludec (Mikhail, 2024). Similar data are not presented for efsitora alfa.

According to research by Ingrasciotta et al. (2024), patients who had previously received basal insulin treatment (ONWARDS 2) and insulin-naive patients (ONWARDS 1, 3, and 5) both demonstrated icodec's superiority over control. Icodec's safety profile is similar to that of basal insulin that is currently on the market. Icodec administered once a week may increase

patient compliance, which could enhance quality of life and treatment satisfaction, particularly in type 2 diabetics who are insulin naive.

CONCLUSION

Overall, both insulin Efsitora Alfa and insulin Icodec represent significant advances in *diabetes* management, with the potential to improve patient adherence through reduced injection frequency. Both demonstrated comparable efficacy in glycemic control (reduction in HbA1c and TIR) compared with daily basal insulin. The main difference lies in the hypoglycemia safety profile. Insulin Efsitora Alfa exhibits similar hypoglycemia rates to insulin glargine U100, even under provocation, making it an attractive option for patients prone to hypoglycemia. On the other hand, insulin Icodec, although effective in lowering HbA1c, is associated with a higher incidence of hypoglycemia, particularly in patients with type 1 diabetes. This needs to be carefully considered in clinical decision-making, and a more cautious dose titration strategy may be necessary for Icodec. Further research, particularly direct comparative studies between Efsitora Alfa and Icodec, will provide a more comprehensive understanding of the optimal position of each insulin in the *diabetes* treatment algorithm.

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