

**Testimony to the FDA
Endocrinologic and Metabolic
Drugs Advisory Committee
Regarding Insulin Icodec for
Diabetes Patients
May 24, 2024**

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(We have no financial conflicts of interest)



FDA Assessment of the Benefits of Insulin Icodec in Adults With Type 1 Diabetes (Based on ONWARDS 6 Trial)

- The efficacy of insulin icodec (a new once-weekly basal insulin) for glycemic control was noninferior to insulin degludec (a proven daily basal insulin) in terms of lower estimated mean changes in glycated hemoglobin (HbA1c) at week 26 of follow-up. However, at week 52 of follow-up, the reduction numerically favored insulin degludec.
- Patient-reported outcomes were not sufficient to support the claim of higher patient satisfaction advantage of insulin icodec.

FDA Assessment of Hypoglycemia Risk for Insulin Icodec in Adults With Type 1 Diabetes

- At week 52, icodec was associated with up to 80% more clinically significant or severe hypoglycemia events compared with degludec.
- The higher icodec-induced hypoglycemia rate also was associated with a higher rate of hypoglycemia-related adverse events.
- Periods of highest risk of icodec-induced hypoglycemia occurred on days 2 to 4, coinciding with the peak glucose-lowering effect of the drug.
- The higher icodec-induced hypoglycemia rate is not exclusively associated with the loading dose or limited to the early titration phase at start of treatment.

Attempt To Find a “Niche” Type 1 Diabetes Population for Icodec?

- FDA considered “exploratory post hoc analyses” to identify type 1 diabetic patients with low glycemic variability as defined as percent coefficient of variation (%CV <36%), who had hypoglycemia risk comparable to the entire cohort of patients on insulin degludec, patients without a history of recurrent severe hypoglycemia or hypoglycemia awareness.
- Agency seems to propose use of continuous glucose monitoring in type 1 diabetes users of icodec users.
- Agency also is considering alternative dose-titration strategies (for bolus insulin during days 2 & 4 of weekly icodec injections) that were not tested in clinical studies.

Issues With the FDA Approach

- ONWARDS 6 excluded individuals with comorbidities or hypoglycemia unawareness, limiting its generalizability.
- Instead of extrapolating data from this trial, the FDA should require Novo to conduct a new trial that addresses its concerns.
- The agency should not just rely on simulation models and post hoc exploratory analysis data in its approval of icodec.
- Real-world experience should not be the arbiter for the safety of icodec.

Other Issues With the FDA Approach

- FDA should consider benefit-risk of icodec in both type 1 and type 2 diabetes because icodec is not “peakless” at its proposed once-weekly dose.
 - Numerous factors (such as fasting, exercise, illness, infections, menstruation, and surgery) pose challenges for icodec dosing and affect the frequency and intensity of hypoglycemia. These factors were not investigated in clinical trials.
- Hypoglycemia was not studied as a primary outcome in any of the ONWARDS trials. Therefore, any lack of statistically significant differences between hypoglycemia and comparator basal insulins in type 2 diabetes trials do not necessarily reflect a lack of clinical effect.

Issues Not Raised in FDA Document

- Open-label design used in most ONWARDS trials may have impacted dose adjustments as well as reporting/monitoring of hypoglycemia adverse events.
 - “[B]ecause participants were permitted to adjust their bolus dose without input from a trial investigator, the knowledge of which treatment they were receiving could have affected any dose adjustments.”
- Higher satisfaction claim for icodec was not adequately supported. In fact, in ONWARDS 6, “there was a statistically significant treatment difference in [favor] of degludec in... total treatment satisfaction score from baseline to weeks 26 and 52.”

Other Concerns From ONWARDS Trials

- Modest weight gain among icodec users in some trials.
- More data are needed regarding the risk of diabetic retinopathy (higher rates in icodec users in ONWARDS 3).
- Immunological events (formation of neutralizing insulin antibodies) have not been studied adequately.
- Hypersensitivity (resulting in swelling of face and lips, as well as urticaria) has been observed across the phase 3a studies in insulin-icodec treated diabetic subjects.
- Missing information regarding icodec use in pregnancy/lactation and elderly patients aged 75 or older.

Other Considerations

- Icodec dosing cannot simply be extrapolated from the current once-daily insulin treatments. Empirically tested alternative icodec titration strategies need to be developed for both types of diabetes.
 - Simple and well-evidenced titration regimens for insulin products are needed.
- Long-term studies (longer than one year) are needed to assess diabetes and cardiovascular outcomes related to use of icodec relative to proven daily basal insulins.
- Information regarding use of icodec in the hospital setting is missing.
- Icodec seems useless for users of automated insulin delivery systems.

Profit-Driven Motives

- As basal insulin prices go down, Novo Nordisk is discontinuing its older, proven daily basal insulin detemir (LEVEMIR), shifting its marketing strategy towards insulin icodec to force as many diabetes patients as possible to switch to its more lucrative icodec.

Conclusions

- Diabetic patients would not be served by premature approval of inadequately tested new insulins. These patients can already be well managed using available proven once-daily basal insulins.
- Public Citizen urges the advisory committee to vote “No” on the question regarding whether the applicant demonstrated that the benefits of insulin icodec outweigh its risks for improving glycemic control in adults with type 1 diabetes.
- The FDA should set a high bar for approval of ultra-long-term insulins by requiring new clinical trials to address the unresolved safety issues for icodec use in diabetic patients.