Testimony Before the Food and Drug Administration's (FDA's) Endocrinologic and Metabolic Drugs Advisory Committee Regarding the Safety and Efficacy of Insulin Icodec in Diabetic Patients

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May 24, 2024

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To contextualize our position, I would like to start by the FDA's summary of the benefits versus hypoglycemia risks of insulin icodec (hereafter, icodec), a new ultra-long-acting insulin analog biological drug proposed by Novo Nordisk to improve glycemic control in adults with diabetes mellitus. I also will discuss other important considerations from the literature.

The FDA assessment focused on insulin icodec's use in type 1 diabetes only, based on findings from the ONWARDS 6 trial,[1] the only phase 3 trial conducted by the sponsor in this patient population.

Efficacy

- The efficacy of icodec for glycemic control was noninferior to insulin degludec (hereafter, degludec), a proven daily basal insulin, in terms of lower estimated mean changes in glycated hemoglobin (HbA1c) at week 26 of follow-up.[2] However, at week 52 of follow-up, the reduction numerically favored degludec.
- Patient-reported outcomes were not sufficient to support the claim of higher patient satisfaction for insulin icodec.[3]

Hypoglycemia risk

- At week 52, icodec was associated with up to 80% more clinically significant or severe hypoglycemia events than degludec.[4]

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[1] Russell-Jones D, Babazono T, Cailleteau R, et al. 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, randomised, open-label, treat-to-target trial. *Lancet*. 2023;402(10413):1636-1647.
[2] Food and Drug Administration. FDA briefing document, the safety and efficacy of biologics license application 761326 for NNC0148-0287 injection (insulin icodec); Endocrinologic and Metabolic Drugs Advisory Committee Meeting. https://www.fda.gov/media/178821/download. Accessed May 24, 2024. PDF p. 20.
[3] *Ibid*. PDF p. 9.
[4] *Ibid*. PDF p. 43.

- The higher icodec-induced hypoglycemia rate also was associated with a higher rate of hypoglycemia-related adverse events.[5]
- 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.

As discussed below, the FDA briefing document seems to be framed so as to attempt to find a niche type 1 diabetes population for icodec.

Proposed labeling language to mitigate hypoglycemia risk[6]

- The FDA considered "exploratory post hoc analyses" to identify type 1 diabetes patients with low glycemic variability (defined as percent coefficient of variation [%CV <36%]) and patients without a history of recurrent severe hypoglycemia or hypoglycemia awareness.
- The FDA seems to propose use of continuous glucose monitoring for patients with type 1 diabetes who use icodec.
- The FDA also is considering alternative dose-titration strategies (for bolus insulin during days 2 and 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 to the wider type 1 diabetes population.
- Instead of extrapolating data from this trial, the FDA should require the sponsor to conduct a new trial that addresses its concerns with data, not with potential approaches that have not been validated in clinical studies.
- Specifically, the agency should not rely on simulation models and post hoc exploratory analysis data.
- Real-world experience should not be the arbiter for the safety of icodec.
- The FDA should consider the benefit-risk profile of icodec for both type 1 and type 2 diabetes because icodec is not "peakless" at its proposed once-weekly dose.[7]
    - 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.

[5] *Ibid*. PDF p. 43.
[6] *Ibid*. PDF p. 43-44.
[7] *Ibid*. PDF p. 12.

- Hypoglycemia was not studied as a primary outcome in any of the six ONWARDS phase 3 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."[8]

Issues not raised by the FDA

- Open-label design used in most ONWARDS trials, which may have influenced 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."[9]
- The 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."[10]

Other Concerns From ONWARDS Trials

- Modest weight gain among icodec users in some trials.[11]
- More data are needed regarding the risk of diabetic retinopathy (higher rates in icodec users in ONWARDS 3).[12]
- Immunological events (formation of neutralizing insulin antibodies) have not been studied adequately.[13]

[8] Lingvay I, Asong M, Desouza C, et al. Once-weekly insulin icodec vs once-daily insulin degludec in adults with insulin-naive type 2 diabetes: The ONWARDS 3 randomized clinical trial. *JAMA*. 2023;330(3):228-237.
[9] Mathieu C, Ásbjörnsdóttir B, Bajaj HS, et al. Switching to once-weekly insulin icodec versus once-daily insulin glargine U100 in individuals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): a phase 3a, randomised, open-label, multicentre, treat-to-target, non-inferiority trial. *Lancet*. 2023;401(10392):1929-1940.
[10] Russell-Jones D, Babazono T, Cailleteau R, et al. 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, randomised, open-label, treat-to-target trial. *Lancet*. 2023;402(10413):1636-1647.
[11] Philis-Tsimikas A, Asong M, Franek E, et al. Switching to once-weekly insulin icodec versus once-daily insulin degludec in individuals with basal insulin-treated type 2 diabetes (ONWARDS 2): a phase 3a, randomised, open label, multicentre, treat-to-target trial. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425.
[12] Lingvay I, Asong M, Desouza C, et al. Once-weekly insulin icodec vs once-daily insulin degludec in adults with insulin-naive type 2 diabetes: The ONWARDS 3 randomized clinical trial. *JAMA*. 2023;330(3):228-237.
[13] Novo Nordisk. Risk management plan summary: insulin icodec (Awiqli). April 30, 2024. https://www.swissmedic.ch/dam/swissmedic/de/dokumente/marktueberwachung/rmp/insulin_icodec_awiqli_rmp-summary.pdf.download.pdf/insulin%20icodec_Awiqli_Risk-Management%20System%20-%20RMP%20Summary%20v0.pdf. Accessed May 23, 2024.

- Hypersensitivity (resulting in swelling of face and lips, as well as urticaria) has been observed across phase 3a studies in subjects with diabetes receiving insulin icodec.[14]
- Missing information regarding icodec use in pregnancy/lactation and elderly patients aged 75 or older.[15]

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 inappropriate 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),[16] shifting its marketing strategy towards icodec to force as many diabetes patients as possible to switch to its more lucrative drug icodec.

Conclusions

- Diabetic patients would not be served by premature approval of inadequately tested new insulins, such as icodec. 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 voting question regarding whether the applicant demonstrated that the benefits of icodec outweigh its risks for improving glycemic control in adults with type 1 diabetes. This issue also applies to type 2 diabetes patients.
- 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.

[14] *Ibid*.
[15] *Ibid*.
[16] Fick M, Aboulenein A, Adler L. Novo Nordisk to discontinue Levemir insulin in U.S. market. November 8, 2023. https://www.reuters.com/business/healthcare-pharmaceuticals/novo-nordisk-discontinue-levemir-insulin-us-market-2023-11-08. Accessed May 23, 2024.