CLOSER LOOK

MEMORANDUM

FDA decision for Novo Nordisk's IDegLira (insulin degludec/liraglutide) delayed three months until December 2016 - September 6, 2016

Executive Highlights

- We got word late Friday that the FDA has extended the regulatory review period for Novo Nordisk's IDegLira (insulin deglude/liraglutide) by three months, with an expected decision by December 2016.
- Novo Nordisk management shared that the news was "due to a technicality" that Novo Nordisk has a solution for and "no additional data or trials are requested."
- This puts the race for the first-to-market basal/GLP-1 between Novo Nordisk and Sanofi back to neck and neck.
- Also last week, the European Commission approved an expanded indication for IDegLira (trade name Xultophy) to include patients with moderate renal impairment in Europe.

Novo Nordisk announced late last Friday that the FDA has extended the regulatory review period for its IDegLira (a fixed-ratio combination dose of new basal insulin Tresiba and the company's top-selling GLP-1 agonist Victoza) by three months. The delay puts the timeline for the expected decision at December 2016, just behind the November 2016 expected timeline for an FDA decision on competitor Sanofi's basal insulin/ GLP-1 agonist combination. The Novo Nordisk press release was sent at about 5:45 pm Friday afternoon EST, and just before midnight CET (central European time), an unusual time for a press release from the Danish giant. Presumably the company had just found out and was working to get the news out before the official start of the long weekend in the US.

Details are scarce on the reason behind the delay, but management shared with us over the long weekend that the news stemmed from a technicality that the company has a solution for, emphasizing that no additional data or trials are requested. The extended review timeline comes as a surprise given the recent 16-0 unanimous FDA Advisory Committee vote in favor of approval. We're curious if the delay is due to the lack of units for the combination product (e.g., a dose of 50 units of insulin degludec/1.8 mg liraglutide is simply "50") that several panelists on the Advisory Committee raised as a potential concern. iGlarLixi's submission, on the other hand, chose to define units based solely on the number of insulin units without referring to the lixisenatide dose, which panelists also felt may be confusing for patients and providers. *Consistency in dosing nomenclature between the two products would likely be helpful, though we would've hoped that potential nomenclature concerns could have been addressed with the FDA prior to submission or addressed post-submission without a delay in approval.*

This has certainly been a topsy-turvy time of getting these basal/GLP-1 combos out onto the US market - as a reminder, Sanofi also announced in late August that the FDA decision on iGlarLixi (the Sanofi basal/ GLP-1 combo of insulin glargine and lixisenatide) has been delayed three months. IDegLira is approved in the EU under the trade name Xultophy, though sales have been on the lighter side compared to what we had anticipated, even though sales of Novo Nordisk's Tresiba (and Sanofi's Toujeo) have been strong, particularly in 2Q16 when both began to gain more traction. We suspect the issue is payers. We had hoped they would see the potency and ease of use of both compounds and that they would understand the value of starting patients earlier on appropriate therapy where the duration of use could be significantly longer - so that patients wouldn't have to stop and start various medications over time. We'll be continuing to watch this market closely and we expect both combo products to receive FDA approval this year.

- **In addition to the unanimous Advisory Committee vote in favor of approval, all patients, patient advocates, and providers argued unanimously for approval during the Open Public Hearing portion of the meeting as well - a testament to the need and anticipation for the combination product.** Members of the public highlighted the benefits of a single combination injection both from a patient convenience and ease of dosing burden perspective and from an affordability perspective. AACE's Dr. Stanley Schwartz and endocrinologist Dr. Paul Norwood praised the combination's strong clinical profile (including the potential to decrease basal insulin doses, reduce risk of hypoglycemia, avoid weight gain, and reduce glycemic variability) while several patients and our very own Ms. Kelly Close spoke to the quality of life benefits of IDegLira. The Advisory Committee panel echoed many of these sentiments in their votes in favor of approval, acknowledging that the single injection aspect of the combination is huge and could encourage greater patient acceptance than attempting to initiate two separate injectable therapies.
- **In more positive news, Novo Nordisk also announced last Thursday that the European Commission has expanded the indication of Xultophy to include patients with moderate renal impairment.** Under the expanded indication, patients with CrCl as low as 30-59 ml/min are eligible for Xultophy therapy. The expanded indication applies to all 28 EU member states, Norway, and Iceland. The expansion is based on the results of the phase 3 LIRA-RENAL trial of liraglutide in patients with moderate renal impairment, which found superior A1c reductions (-1.0% vs. 0.4%), weight loss (-2.4 kg vs. -1.1 kg), and systolic blood pressure reductions (-2.45 mm Hg vs. 0.33 mm Hg) with standalone liraglutide (Victoza) vs. placebo in this patient population. Importantly, treatment with Victoza did not lead to any worsening of renal impairment, as there was no significant difference between the groups on measures related to renal function (eGFR and urinary albumin/creatinine). These results previously supported an expanded indication for Victoza in moderate renal impairment as well.

Close Concerns Questions

Q: Where there any common concerns that contributed to the decision delays for IDegLira and iGlarLixi?

Q: Will the specific reason for the delay be made public eventually?

Q: How might this delay, and the requested additional information, impact IDegLira's US label in comparison to the EU label?

Q: Will the LIRA-RENAL results be included on IDegLira's US label or will Novo Nordisk have to pursue an indication expansion at a future date?

Q: What role might Novo Nordisk's new management structure play in reacting to the announcement of the decision delay? Will former head of US Mr. Jesper Høiland continue to work closely with new head of US Mr. Jakob Riis on the response?

Q: How quickly is Novo Nordisk prepared to launch the product following a potential FDA approval in December?

Q: IDegLira may receive approval around the same time as next-generation rapid-acting insulin Faster aspart - how might resources and attention be allocated toward the dual launches?

Q: How might the delay in FDA decisions impact formulary positioning and negotiations for both IDegLira and iGlarLixi for 2017?

Q: Will payers potentially view IDegLira (and iGlarLixi) less favorably in light of these FDA decision delays?

Q: This is the third in a string of recent decision delays from the FDA (first on a decision on an expanded indication for Lilly/BI's Jardiance and second on iGlarLixi) - is this reflective of an increasingly complex diabetes field or perhaps limited resources at the agency?

Q: How common are delays in FDA decisions across all of its divisions (including outside of diabetes)? Should we expect more of these for particularly complex submissions moving forward?

-- by Helen Gao and Kelly Close