CLOSER LOOK

MEMORANDUM

Novo Nordisk submits SWITCH 1 and 2 hypoglycemia data to FDA for inclusion on Tresiba (insulin degludec) label - September 27, 2016

Executive Highlights

- Novo Nordisk submitted a supplemental application to the FDA for the inclusion of phase 3b SWITCH 1 and 2 results on the label for Tresiba (insulin degludec).
- SWITCH 1 and 2 demonstrated significant reductions in severe or blood glucose-confirmed symptomatic hypoglycemia and nocturnal hypoglycemia with Tresiba therapy compared to standard-of-care Lantus (insulin glargine).
- Assuming a 12-month review cycle, a decision is expected by the end of September 2017.

Novo Nordisk announced last Friday that it has submitted a supplemental application to the FDA for the inclusion of the phase 3b SWITCH 1 and 2 results on the label for its next-generation basal insulin Tresiba (insulin degludec). The SWITCH 1 and 2 trials demonstrated significant reductions in severe or blood glucose-confirmed symptomatic hypoglycemia and nocturnal hypoglycemia with Tresiba therapy compared to Sanofi's Lantus (insulin glargine) in patients with type 1 and type 2 diabetes, respectively. We expect Novo Nordisk is seeking an expanded indication for Tresiba to reflect this hypoglycemia benefit over standard of care Lantus. Assuming a standard 10-month review cycle, a decision is expected by the end of July 2017.

Earlier meta-analyses of Tresiba's clinical data had suggested a potential reduction in hypoglycemia - a product of Tresiba's ultra-long and flat profile of action (up to 42 hours with hardly any peak in PK/PD studies). However, throughout Tresiba's complicated regulatory process, the FDA remained very skeptical about the product's actual benefit on hypoglycemia and no hypoglycemia claim eventually made it on to the label when Tresiba was approved last September. The SWITCH 1 and 2 studies were designed in close collaboration with the FDA to more clearly demonstrate a hypoglycemia benefit for Tresiba - a delicate and difficult feat to be sure. The trials involved an unusual crossover design in which participants were randomized to either Tresiba or Lantus therapy initially before switching to the other therapy halfway through the trial. As such, participants served as their own controls in the trials. Beyond the demonstrable reductions in hypoglycemia, data from SWITCH 2 presented at EASD 2016 suggested that patients on Tresiba experienced greater improvements in a variety of patient-reported quality-of-life metrics, including daily function, diabetes management, emotional well-being, sleep disruption, and work productivity.

- **The inclusion of a hypoglycemia benefit on Tresiba's label would be a major win for Novo Nordisk as it endeavors to differentiate the product from older basal insulin analogs.** While Tresiba's efficacy, as measured by A1c, is non-inferior but not superior to Lantus, the newer insulin offers several meaningful clinical advantages that may offer patients greater safety, flexibility, and dosing convenience. Tresiba's current label is headlined by a flexible-dosing claim, which allows patients to take Tresiba at any time of the day as long as it is at least eight hours before the next dose of Tresiba (thus, a patient who forgets his daily morning dose of Tresiba has the flexibility to take that same dose later in the day). We've heard clinical experts such as Dr. Anne Peters rave about the benefits of this flexibility for her patients. Furthermore, Tresiba was associated with a reduction in insulin dose in phase 3 trials compared to Lantus and its extremely long and flat profile of action has led some such as Indiana University's Dr. Richard DiMarchi to suggest that we're nearing the end of the road in terms our ability to improve the pharmacokinetics of insulin. We expect the potential addition of a hypoglycemia benefit to the label would be a major boon as Novo Nordisk continues to negotiate the product's formulary positioning and reimbursement with

payers. Tresiba's most direct competitor, Sanofi's next-generation basal insulin Toujeo (U300 insulin glargine), does not have either a hypoglycemia benefit or flexible dosing claim on its label.

-- by Helen Gao and Kelly Close