Rybelsus® (semaglutide) – New drug approval

- On September 20, 2019, the FDA announced the approval of Novo Nordisk's Rybelsus (semaglutide), as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
    - Rybelsus is not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans.
    - Rybelsus has not been studied in patients with a history of pancreatitis. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.
    - Rybelsus is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis, as it would not be effective in these settings.
- Rybelsus is the first oral glucagon-like peptide-1 (GLP-1) receptor agonist. Previously approved GLP-1 receptor agonists require subcutaneous injections.
    - Semaglutide is also available as injectable Ozempic®. Ozempic shares the same indication as Rybelsus.
- The efficacy of Rybelsus was evaluated in several clinical studies as monotherapy and in combination with metformin, sulfonylureas, sodium glucose co-transporter-2 (SGLT-2) inhibitors, insulins, and thiazolidinediones in patients with type 2 diabetes. The efficacy of Rybelsus was compared with placebo, Jardiance® (empagliflozin), Januvia® (sitagliptin), and Victoza® (liraglutide). The primary endpoint in the studies was a reduction in HbA_{1c}.
    - Throughout the clinical studies, Rybelsus provided a clinically significant reduction from baseline in HbA_{1c} vs. placebo.
    - Treatment with Rybelsus 14 mg resulted in a statistically significant reduction in HbA_{1c} vs. Jardiance 25 mg (-1.3 vs. -0.9, respectively; $p < 0.001$)
    - Treatment with Rybelsus 7 mg and 14 mg resulted in a statistically significant reduction in HbA_{1c} compared to Jardiance 100 mg (-1.0 and -1.3 vs. -0.8, respectively; $p < 0.001$).
    - Treatment with Rybelsus 14 mg resulted in non-inferior reductions in HbA_{1c} vs. Victoza 1.8 mg (-1.2 vs. -1.1, respectively).
- In addition, Rybelsus was evaluated in a double-blind, placebo-controlled, cardiovascular outcomes trial (PIONEER 6) in 3,183 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease. Patients were randomized to Rybelsus or placebo, both in addition to standard of care, for a median observation time of 16 months. The primary endpoint was the time to first occurrence of a three-part composite outcome of major adverse cardiovascular events (MACE) which included cardiovascular death, non-fatal myocardial infarction and nonfatal stroke.
    - The total number of primary component MACE endpoints was 137 (61 [3.8%] with Rybelsus vs. 76 [4.8%] with placebo). No increased risk for MACE was observed with Rybelsus.
    - The FDA is still reviewing Novo Nordisk's application for Rybelsus seeking an additional indication to reduce the risk of MACE in adults with type 2 diabetes mellitus and established cardiovascular disease. A decision is expected in 1Q 2020.
- Rybelsus carries a boxed warning for risk of thyroid C-cell tumors.

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- Rybelsus is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 or a known hypersensitivity to semaglutide or to any of the components in Rybelsus.

- Additional warnings and precautions for Rybelsus include pancreatitis, diabetic retinopathy complications, hypoglycemia with concomitant use of insulin secretagogues or insulin, acute kidney injury, and hypersensitivity.

- The most common adverse reactions (≥ 5%) with Rybelsus use were nausea, abdominal pain, diarrhea, decreased appetite, vomiting and constipation.

- The recommended initial dose of Rybelsus is 3 mg orally once daily for 30 days. The 3 mg dose is intended for treatment initiation and is not effective for glycemic control. After 30 days on the 3 mg dose, the dose should be increased to 7 mg once daily.

    — The dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose. Taking two 7 mg Rybelsus tablets to achieve a 14 mg dose is not recommended.
    — Patients should be instructed to take Rybelsus at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only.

- Novo Nordisk plans to launch Rybelsus beginning in 4Q 2019. Rybelsus will be available as 3 mg, 7 mg, and 14 mg tablets.

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