Oral Semaglutide

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Introduction

Oral semaglutide (Rybelsus) is the first oral glucagon-like peptide 1 (GLP-1) receptor agonist product approved by the U.S. Food and Drug Administration (FDA) for the treatment of type 2 diabetes (1). As a class, GLP-1 receptor agonists are widely used and recommended for the management of type 2 diabetes. The American Diabetes Association's *Standards of Medical Care in Diabetes—2019* recommend GLP-1 receptor agonists with proven cardiovascular benefit as one of the two preferred options for add-on therapy in patients with type 2 diabetes and established atherosclerotic cardiovascular disease after metformin and lifestyle intervention (2). Drugs in this class are likewise generally recommended as add-on therapy after metformin in patients not meeting individualized glycemic goals when there is a compelling need to minimize hypoglycemia or promote weight loss (2). Despite their clinical benefits, GLP-1 receptor agonists historically have required self-administration by subcutaneous injection. The availability of oral semaglutide provides a new option within the class for patients who are unable or unwilling to self-administer an injectable agent.

Indication

Oral semaglutide received FDA approval in September 2019 for use as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (1). The product is available in 3-, 7-, and 14-mg tablets. The manufacturer recommends initiating oral semaglutide at the 3-mg dose once daily and then increasing the dose to 7 mg once daily after 30 days. For patients requiring additional glycemic lowering, the dose can be further increased to 14 mg once daily after at least 30 days at the 7-mg dose (1). The manufacturer has filed an application with the FDA for a second indication to reduce major adverse cardiovascular events (MACE) in adults with type 2 diabetes and established cardiovascular disease (3). According to a manufacturer press release, the FDA review for the MACE indication is expected to be completed in the first quarter of 2020 (3).

Mechanism of Action

GLP-1 receptor agonists work to lower glycemia via several mechanisms, including stimulation of glucose-dependent insulin secretion from pancreatic β-cells, suppression of glucagon secretion from pancreatic α-cells, and delaying of gastric emptying (4). The novelty of oral semaglutide is in the formulation that allows for oral administration and absorption of the drug. Oral semaglutide is coformulated with the absorption enhancer sodium *N*-(8-[2-hydroxylbenzoyl] amino) caprylate (SNAC) (5). Coformulation with SNAC helps facilitate semaglutide absorption in the stomach by increasing the local pH, which leads in turn to increased drug solubility and protection against proteolytic degradation (6).

Potential Advantages

The primary advantage of this semaglutide formulation is its oral administration route, which makes it an option for patients who are unwilling or unable to self-inject glucose-lowering medications. Oral administration does not appear to diminish the glucose- or weight-lowering efficacy of the agent, as demonstrated in the PIONEER 4 study (7). PIONEER 4 compared the addition of oral semaglutide or subcutaneous liraglutide to background metformin with or without a sodium–glucose cotransporter 2 (SGLT2) inhibitor in patients with type 2 diabetes and a baseline A1C of 7.0–9.5%. After 26 weeks of treatment, oral semaglutide (target dose of 14 mg once daily) resulted in a mean A1C reduction from baseline of 1.2% compared with a reduction of 1.1% observed with liraglutide (target dose of 1.8 mg once daily), thus demonstrating noninferiority. In terms of weight loss, mean weight reductions from baseline of 4.4 and 3.1 kg were seen in the oral semaglutide and liraglutide groups, respectively (P = 0.0003) (7).

Oral semaglutide has likewise compared favorably when studied against the SGLT2 inhibitor empagliflozin (8). The PIONEER 2 trial enrolled patients with type 2

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diabetes uncontrolled on metformin (baseline A1C 7.0–10.5%). Participants were randomized to receive either oral semaglutide 14 mg once daily or empagliflozin 25 mg once daily. At 26 weeks, oral semaglutide treatment resulted in a superior reduction in mean A1C from baseline when compared with empagliflozin (–1.3 vs. –0.9%, $P < 0.0001$). Oral semaglutide additionally demonstrated better weight loss at week 52 when compared with empagliflozin treatment (–4.7 vs. –3.8 kg, $P = 0.0114$) (8).

Potential Disadvantages

As with all agents in the GLP-1 receptor agonist class, oral semaglutide is associated with gastrointestinal adverse reactions such as nausea, abdominal pain, and vomiting (1). Although oral administration is a potential advantage with this product, current recommendations for administration may prove difficult for some patients. It is recommended that oral semaglutide be administered at least 30 min before the first food, beverage, or other oral medications of the day and that it be taken with no more than 4 oz plain water only (1). The prescribing information warns that not following these directions will lessen the effect of the medication. These instructions may prove difficult for some patients, particularly if they are taking other oral medications that are recommended to be taken first thing in the morning on an empty stomach, such as levothyroxine or bisphosphonates. Furthermore, the prescribing information notes that, when coadministered with thyroxine, the total exposure (area under the curve) of thyroxine was increased by 33% (1), indicating that coadministration could result in excessive thyroxine levels. Accordingly, the manufacturer suggests that increased clinical or laboratory monitoring be considered for medications with a narrow therapeutic index when taken concomitantly with oral semaglutide.

Cost

At the time of this writing, the published average wholesale price (AWP) for oral semaglutide was $30.89 per tablet (all doses), equating to a monthly cost of $926.92 (9). It should be noted that the listed AWP does not account for discounts, rebates, or other price adjustments often involved in prescription sales that affect the actual cost incurred by patients (2). As a basis for comparison, the published monthly AWP price for oral semaglutide is the same as the published monthly AWP price for the once-weekly injectable semaglutide formulation (Ozempic) (9).

Commentary

Oral semaglutide, while not the first agent in its class, is the first orally administered GLP-1 receptor agonist on the market. In our opinion, this is a welcome addition and provides an additional option for patients and providers. However, although oral administration may be an advantage for some patients, the need to take the medication on an empty stomach may prove a barrier for others.

Bottom Line

Oral semaglutide, the first oral GLP-1 receptor agonist on the market, has compared favorably in clinical trials against other glucose-lowering agents in adults with type 2 diabetes. Time will tell if this agent will also receive a cardiovascular indication and how it will be incorporated into routine clinical practice.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Both authors contributed to and were involved in the research, writing, and editing of this article. J.J.N. is the guarantor of this work and, as such, had full access to all of the references cited and takes responsibility for the accuracy of the content.

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