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A Cardiovascular Indication for Oral Semaglutide *(Rybelsus)*

The oral glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide (*Rybelsus* – Novo Nordisk), which was approved by the FDA in 2019 for treatment of type 2 diabetes in adults, has now also been approved to reduce the risk of major adverse cardiovascular events (MACE) in adults with type 2 diabetes who are at high risk for these events.[1] The injectable GLP-1 receptor agonists semaglutide *(Ozempic)*, dulaglutide (*Trulicity),* and liraglutide *(Victoza)* are also approved for cardiovascular risk reduction in patients with type 2 diabetes (see Table 1).[2]

CLINICAL STUDIES — FDA approval of oral semaglutide for the new indication was based on the results of a double-blind trial (SOUL) in 9650 patients ≥50 years old with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), or both. About 87% of patients had cardiovascular disease at enrollment. Patients were randomized to receive oral semaglutide titrated to 14 mg once daily or placebo in addition to standard care (other glucose-lowering and cardiovascular risk-reducing drugs). After a median of 49.5 months, the incidence of MACE (a composite of nonfatal myocardial infarction [MI], nonfatal stroke, or cardiovascular death), the primary endpoint, was statistically significantly lower in the semaglutide arm compared to the placebo arm (12.0% vs 13.8%; HR 0.86, 95% CI 0.77-0.96 [number needed to treat 55.6]). The reduction was primarily driven by a reduction in nonfatal MI (HR 0.74, 95% CI 0.61-0.89). Cardiovascular mortality and adverse kidney outcomes were similar in both groups.[3]

DOSAGE, ADMINISTRATION, AND COST — *Rybelsus* is available in two formulations (R1 and R2). The R1 formulation, which is available in 3-, 7-, and 14-mg tablets, should be used for the new indication. Slow titration of the dose can reduce GI adverse effects and improve tolerability. The recommended starting dosage is 3 mg once daily for 30 days; the dose should be increased to 7 mg once daily for 60 days and, if needed for glycemic control, to 14 mg once daily thereafter. All patients in the SOUL trial were titrated to a semaglutide dose of 14 mg. *Rybelsus* should be taken on an empty stomach in the morning with no more than 4 ounces of plain water. The wholesale acquisition cost (WAC) for a 30-day supply of *Rybelsus* is $997.60.[4]

CONCLUSION — Addition of the oral glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide *(Rybelsus)* to standard treatment reduced the risk of a major adverse cardiovascular event (MACE) in adults with type 2 diabetes and atherosclerotic cardiovascular disease and/or chronic kidney disease. *Rybelsus* has not been directly compared with injectable GLP-1 receptor agonists for this indication. ■

Table 1. FDA-Approved CV and Renal Indications for GLP-1 Receptor Agonists in Patients with Type 2 Diabetes

Dulaglutide *(Trulicity)*
► Reduce risk of MACE in adults with type 2 diabetes and established CVD or multiple CV risk factors
Liraglutide *(Victoza)*
► Reduce risk of MACE in adults with type 2 diabetes and established CVD
Semaglutide, SC *(Ozempic)*
► Reduce risk of MACE in adults with type 2 diabetes and established CVD
► Reduce risk of sustained eGFR decline, end-stage kidney disease, and CV death in adults with type 2 diabetes and CKD
Semaglutide, PO *(Rybelsus)*
► Reduce the risk of MACE in adults with type 2 diabetes who are at high risk for these events

CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; MACE = major adverse cardiovascular events

Additional Content Available Online

Comparison Chart: GLP-1 and GIP/GLP-1 Receptor Agonists for Type 2 Diabetes
https://medicalletter.org/TML-article-1742c

1. Oral semaglutide (Rybelsus) for type 2 diabetes. Med Lett Drugs Ther 2019; 61:166.
2. Non-insulin drugs for type 2 diabetes. Med Lett Drugs Ther 2025 in press.
3. DK McGuire et al. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. N Engl J Med 2025; 392:2001.

4. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. November 5, 2025. Reprinted with permission by First Databank, Inc. All rights reserved. ©2025. www.fdbhealth.com/policies/drug-pricing-policy.

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