semaglutide (Rybelsus®)

Classification
Antidiabetic agent

Pharmacology
Semaglutide is a human glucagon-like peptide 1 (GLP-1) receptor agonist (incretin mimetic). Semaglutide activates the GLP-1 receptor in pancreatic beta cells leading to glucose-dependent insulin release. It also decreases glucagon secretion, slows gastric emptying, and promotes satiety. Oral semaglutide is co-formulated with the absorption enhancer salcaprozate sodium.

Indication
RYBELSUS is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use:
- 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.
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not indicated for use in patients with type 1 diabetes mellitus.

Pharmacokinetics

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Occurs in stomach. Co-formulated with salcaprozate sodium to facilitate absorption. Bioavailability = 0.4%-1%</td>
</tr>
<tr>
<td>Distribution</td>
<td>&gt;99% bound to albumin</td>
</tr>
<tr>
<td>Pharmacokinetic Parameter</td>
<td>Details</td>
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<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td>Metabolism</td>
<td>Proteolytic cleavage of peptide backbone, beta-oxidation of fatty acid side chain; half life = 1 week</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine, feces. 3% of absorbed dose excreted in urine as intact semaglutide.</td>
</tr>
</tbody>
</table>

**Dosage/Administration**

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. Waiting less than 30 minutes, or taking RYBELSUS with food, beverages (other than plain water) or other oral medications will lessen the effect of RYBELSUS by decreasing its absorption. Waiting more than 30 minutes to eat may increase the absorption of RYBELSUS.

Swallow tablets whole. Do not split, crush, or chew tablets.

Start with 3 mg 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, increase the dose to 7 mg once daily. 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. If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day.

**Switching Patients between Ozempic and Rybelsus:**

Patients treated with Rybelsus 14 mg daily can be transitioned to Ozempic subcutaneous injection 0.5 mg once weekly. Patients can start Ozempic the day after their last dose of Rybelsus.

Patients treated with once weekly Ozempic 0.5 mg subcutaneous injection can be transitioned to Rybelsus 7 mg or 14 mg. Patients can start Rybelsus up to 7 days after their last injection of Ozempic. There is no equivalent dose of Rybelsus for Ozempic 1 mg.

**Use in Special Population**

**Pregnancy:** Available data with RYBELSUS use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are clinical considerations regarding the
risks of poorly controlled diabetes in pregnancy. Based on animal reproduction studies, there may be potential risks to the fetus from exposure to RYBELSUS during pregnancy. RYBELSUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses and structural abnormalities were observed at exposure below the MRHD (rabbit) and ≥10-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species.

**Lactation:** There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats. Salcaprozate sodium (SNAC), an absorption enhancer in Rybelsus, crosses the placenta and reaches fetal tissues in rats. SNAC and/or its metabolites concentrated in the milk of lactating rats. When a substance is present in animal milk, it is likely that the substance will be present in human milk (see Data). There are no data on the presence of SNAC in human milk. Since the activity of UGT2B7, an enzyme involved in SNAC clearance, is lower in infants compared to adults, higher SNAC plasma levels may occur in neonates and infants. Because of the unknown potential for serious adverse reactions in the breastfed infant due to the possible accumulation of SNAC from breastfeeding and because there are alternative formulations of semaglutide that can be used during lactation, advise patients that breastfeeding is not recommended during treatment with RYBELSUS.

**Females and Males of Reproductive Potential:** Discontinue RYBELSUS in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

**Pediatric Use:** Safety and efficacy of Rybelsus have not been established in pediatric patients (younger than 18 years).

**Geriatric Use:** In the pool of glycemic control trials, 1229 (29.9%) RYBELSUS-treated patients were 65 years of age and over and 199 (4.8%) RYBELSUS-treated patients were 75 years of age and over. In PIONEER 6, the cardiovascular outcomes trial, 891 (56.0%) RYBELSUS-treated patients were 65 years of age and over and 200 (12.6%) RYBELSUS-treated patients were 75 years of age and over.
No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment: The safety and efficacy of RYBELSUS was evaluated in a 26-week clinical study that included 324 patients with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m²). In patients with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed.

No dose adjustment of RYBELSUS is recommended for patients with renal impairment.

Hepatic Impairment: In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed. No dose adjustment of RYBELSUS is recommended for patients with hepatic impairment.

Contraindication

Personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia Syndrome Type 2 (MEN 2).

Prior hypersensitivity reaction to semaglutide or to any of the excipients in Rybelsus. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with Rybelsus.

Precautions

Risk of Thyroid C-Cell Tumors: In mice and rats, semaglutide caused a dose-dependent and treatment-duration dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures. It is unknown whether RYBELSUS causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

RYBELSUS is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with
the use of RYBELSUS and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with RYBELSUS. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

**Pancreatitis:** In glycemic control trials, pancreatitis was reported as a serious adverse event in 6 RYBELSUS-treated patients (0.1 events per 100 patient years) versus 1 in comparator-treated patients (<0.1 events per 100 patient years).

After initiation of RYBELSUS, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, RYBELSUS should be discontinued and appropriate management initiated; if confirmed, RYBELSUS should not be restarted.

**Diabetic Retinopathy Complications:** In a pooled analysis of glycemic control trials with RYBELSUS, patients reported diabetic retinopathy related adverse reactions during the trial (4.2% with RYBELSUS and 3.8% with comparator).

In a 2-year cardiovascular outcomes trial with semaglutide injection involving patients with type 2 diabetes and high cardiovascular risk, diabetic retinopathy complications (which was a 4 component adjudicated endpoint) occurred in patients treated with semaglutide injection (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (semaglutide injection 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (semaglutide injection 0.7%, placebo 0.4%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.
Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin:
Patients receiving RYBELSUS in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Acute Kidney Injury: There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists, including semaglutide. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of RYBELSUS in patients reporting severe adverse gastrointestinal reactions.

Hypersensitivity: Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with RYBELSUS. If hypersensitivity reactions occur, discontinue use of RYBELSUS; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to RYBELSUS.

Anaphylaxis and angioedema have been reported with GLP-1 receptor agonists. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with RYBELSUS.

Acute Gallbladder Disease: Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In placebo-controlled trials, cholelithiasis was reported in 1% of patients treated with RYBELSUS 7 mg. Cholelithiasis was not reported in RYBELSUS 14 mg or placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.
### Adverse Effects

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Placebo (n = 362)</th>
<th>Rybelsus 7 mg (n = 356)</th>
<th>Rybelsus 14 mg (n = 356)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>6</td>
<td>5</td>
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</table>

**Increases in Amylase and Lipase:** Patients exposed to Rybelsus 7 mg and 14 mg had mean increase from baseline in amylase of 10% and 13%, respectively, and lipase of 30% and 34%, respectively. These changes were not observed in placebo-treated patients.

**Monitoring**

Plasma glucose, HbA1c, heart rate and body weight, renal function (especially when initiating therapy or increasing doses in patients reporting severe adverse GI reactions); signs/symptoms of pancreatitis, triglycerides; signs/symptoms of gallbladder disease; worsening of diabetic retinopathy (particularly in those with a prior history of the disease).

**Interactions**

**Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin:** When initiating RYBELSUS, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.

**Oral Medications:** RYBELSUS causes a delay of gastric emptying, and thereby has the potential to impact the absorption of other oral medications. Levothyroxine
exposure was increased 33% when administered with RYBELSUS in a drug interaction study.

When coadministering oral medications instruct patients to closely follow RYBELSUS administration instructions. Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic index or that require clinical monitoring.

**Efficacy**

**PIONEER 6:** In a randomized, double-blind, placebo-controlled trial, Husain and colleagues assessed cardiovascular outcomes of once-daily oral semaglutide. The study’s purpose was to rule out an excess in cardiovascular risk with oral semaglutide in patients with type 2 diabetes.

Patients were at high cardiovascular risk. Inclusion criteria included age > 50 years with established cardiovascular disease or chronic kidney disease or age > 60 with cardiovascular risk factors. Exclusion criteria included treatment with any GLP-1 receptor agonist, dipeptidyl peptidase 4 inhibitor, or pramlintide within 90 days before screening; NYHA class 4 heart failure; planned coronary-artery, carotid-artery, or peripheral-artery revascularization; myocardial infarction, stroke, or hospitalization for unstable angina or TIA within 60 days before screening; long-term or intermittent hemodialysis or peritoneal dialysis, or severe renal impairment (estimated GFR < 30 ml per minute); proliferative retinopathy or maculopathy resulting in active treatment.

3183 patients were randomized to receive once daily semaglutide (n = 1591) or placebo (n = 1592) in addition to standard of care treatment. The target dose of semaglutide was 14 mg. Investigators maintained and intensified patients’ glucose-lowering and cardiovascular medication in accordance with local and international guidelines. A dose escalation schedule was used to decrease gi side effects. Median time in the trial was 15.9 months; 75% of the patients received oral semaglutide or placebo for more than one year.

Sixty-eight (68.4%) of patients were male and 84.7% were >50 and had established cardiovascular disease or chronic kidney disease. At baseline, mean (+ SD) body weight was 90.9 + 21.2 kg, mean HgA1c = 8.2 + 1.6%, mean age 66 + 7 years, mean duration of diabetes 14.9 + 8.5 years.

The primary outcome was time to first occurrence of a major adverse cardiovascular event (composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The primary outcome occurred in 61 of 1591 patients (3.8%) receiving oral semaglutide and 76 of 1592 (4.8%) receiving
placebo (21% difference in risk, HR = 0.79, 95% CI = 0.57 to 1.11, p < 0.001 for noninferiority, p = 0.17 for superiority). Mean change from baseline to end point for HgA1c and body weight were -1.0% (oral semaglutide) versus -0.3% (placebo and -4.2 kg versus -0.8 kg.

Serious adverse events occurred in 301/1591 (18.9%) patients in the oral semaglutide group and 358/1592 (22.5%) patients in the placebo group. These were varied and attributed to several different organ systems. More patients stopped taking oral semaglutide than placebo (11.6% versus 6.5%), mainly because more gi adverse events occurred in the semaglutide versus the placebo group (6.8% versus 1.6%).

Dosage Forms/Cost
Tablets: 3 mg, 7 mg, 14 mg. $884.81 per month. GoodRx.

Special Considerations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pkg Size</th>
<th>Avg Cost</th>
<th>Item Qty</th>
<th>Item Total</th>
</tr>
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<tbody>
<tr>
<td>Ozempic 0.5mg, 1mg</td>
<td>1 multi-dose pen</td>
<td>$892.06</td>
<td>35</td>
<td>$31,222</td>
</tr>
<tr>
<td>Rybelsus 14mg, 7mg, 3mg</td>
<td>30</td>
<td>$892</td>
<td>17</td>
<td>$15,164</td>
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<tr>
<td>Wegoxy 0.5mg, 2.4mg</td>
<td>4</td>
<td>$1349</td>
<td>4</td>
<td>$5,396</td>
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</table>

Summary/Conclusion
In 2019, the FDA approved semaglutide (Rybelsus), the first oral glucagon-like peptide I receptor agonist (GLP-I) as an adjunct to diet and exercise for the treatment of type 2 diabetes. The absorption enhancer salcaprozate sodium aids semaglutide’s absorption through the gastric mucosa, preventing its rapid degradation in the stomach. For Rybelsus to be fully efficacious, it must be taken daily at least 30 minutes before the first food, other beverage, or oral meds of the day with no more than four ounces of water.

In the PIONEER 1 trial, monotherapy with semaglutide 7 mg and 14 mg once daily for 26 weeks resulted in statistically significant reductions in A1c compared with
placebo (-1.2% [95% CI -1.5%, -1%] and -1.4% [95% CI -1.7%, -1.2%], respectively). Semaglutide (Rybelsus) 14 mg also significantly reduced body weight compared to placebo (-2.6 kg [95% CI: -3.4 to -1.8 kg]). In the PIONEER 6 cardiovascular outcomes trial (CVOT), oral semaglutide was non-inferior to placebo with respect to cardiovascular safety; further cardiovascular outcomes trials are in process.

**Recommendation**

Oral semaglutide (Rybelsus) should be added to the formulary.

**References**


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October 28, 2022