Indications and Usage

RYBELSUS® (semaglutide) tablets 7 mg or 14 mg is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

Limitations of Use

• 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. Consider other antidiabetic therapies in patients with a history of pancreatitis

• RYBELSUS® is not indicated for use in patients with type 1 diabetes or for the treatment of patients with diabetic ketoacidosis

Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

• In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant 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

• RYBELSUS® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (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®
Finally! A GLP-1 RA in a once-daily pill

**Comparable A1C reductions with RYBELSUS® 14 mg vs liraglutide 1.8 mg**

**ADDED TO METFORMIN WITH OR WITHOUT SGLT-2i**

**26-WEEK PRIMARY ENDPOINT**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change in A1C from Baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=142; baseline: 7.9%)</td>
<td>-0.2%</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg (n=284; baseline: 8.0%)</td>
<td>-1.1%</td>
</tr>
<tr>
<td>RYBELSUS® 14 mg (n=285; baseline: 8.0%)</td>
<td>-1.2%</td>
</tr>
</tbody>
</table>

**Mean change in body weight**

RYBELSUS® is not indicated for weight loss.

-9.7 lb mean change in body weight from baseline to week 26 for RYBELSUS® 14 mg (Baseline: 204 lb)

-6.8 lb mean change in body weight from baseline to week 26 for liraglutide 1.8 mg (Baseline: 210 lb; ETD -2.6 lb [95% CI, -4.2, -1.3])

-1.1 lb mean change in body weight from baseline to week 26 for placebo (Baseline: 205 lb; ETD -8.4 lb [95% CI, -10.3, -6.6])

**Study design**

PIONEER 4: Head-to-head vs liraglutide 1.8 mg

In a double-blind, double-dummy trial with a primary endpoint of mean change in A1C from baseline to 26 weeks, 711 patients with type 2 diabetes on metformin alone or metformin with an SGLT-2 inhibitor were randomized to RYBELSUS® 14 mg (n=285), liraglutide 1.8 mg subcutaneous injection (n=284), or placebo (n=142), all once daily.

- Confirmatory secondary endpoint: Mean change in body weight to Week 26

42% greater weight reduction with RYBELSUS® 14 mg than liraglutide 1.8 mg

**ETD=estimated treatment difference.**

**Important Safety Information**

**Warnings and Precautions**

- **Risk of Thyroid C-Cell Tumors:** Patients should be further evaluated if serum calcitonin is measured and found to be elevated or thyroid nodules are noted on physical examination or neck imaging

- **Pancreatitis:** Has been reported in clinical trials. 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, discontinue RYBELSUS® and initiate appropriate management; if confirmed, do not restart RYBELSUS®
Superior A1C reduction vs the most-prescribed  
DPP-4i (Januvia®)\(^1\)

**Study design\(^1\,^4\)**  
PIONEER 3: Head-to-head vs Januvia\(^a\)  
In a double-blind, double-dummy trial with a primary endpoint of mean change in A1C from baseline to 26 weeks, 1864 patients with type 2 diabetes on metformin alone or metformin with a sulfonylurea were randomized to RYBELSUS\(^®\) 3 mg (n=466), RYBELSUS\(^®\) 7 mg (n=465), RYBELSUS\(^®\) 14 mg (n=465), or Januvia\(^®\) 100 mg (n=467), all once daily.  
• **Confirmatory secondary endpoint:** Mean change in body weight to Week 26

**Superior A1C reduction vs the most-prescribed  
SGLT-2i (Jardiance\(^®\))\(^1\)**

**Study design\(^1\,^5\)**  
PIONEER 2: Head-to-head vs Jardiance\(^®\)  
In an open-label trial with a primary endpoint of mean change in A1C from baseline to 26 weeks, 822 patients with type 2 diabetes on metformin were randomized to RYBELSUS\(^®\) 14 mg (n=411) or Jardiance\(^®\) 25 mg (n=410), both once daily.  
• **Confirmatory secondary endpoint:** Mean change in body weight to Week 26

**Important Safety Information**  
**Warnings and Precautions**  
• **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 trial with semaglutide injection involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications 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 than among patients without a known history of diabetic retinopathy.

**Important Safety Information**  
**Warnings and Precautions**  
• **Hypoglycemia:** The risk of hypoglycemia is increased when RYBELSUS\(^®\) is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Patients may require a lower dose of the secretagogue or insulin to reduce the risk of hypoglycemia in this setting

---

Superior A1C reduction vs the most-prescribed \(^3\)  
DPP-4i (Januvia\(^®\))\(^1\)

**RYBELSUS\(^®\) 7 mg and 14 mg vs Januvia\(^®\) 100 mg\(^1\,^4\)**  
**ADDED TO METFORMIN WITH OR WITHOUT SULFONYLUREA**  
**26-WEEK PRIMARY ENDPOINT**

### Line Graph

**Mean Change in A1C from Baseline (%)**

- **RYBELSUS\(^®\) 7 mg** (n=465; baseline: 8.1%)  
  - Baseline: 7.0%  
  - 26-week change: -0.8%  
  - **63% Greater A1C Reduction with 14 mg**  

- **RYBELSUS\(^®\) 14 mg** (n=465; baseline: 8.1%)  
  - Baseline: 7.0%  
  - 26-week change: -1.0%  
  - **63% Greater A1C Reduction with 14 mg**  

- **Januvia\(^®\) 100 mg** (n=467; baseline: 8.3%)  
  - Baseline: 7.2%  
  - 26-week change: -0.8%  

**p<0.001 vs Januvia\(^®\)**

---

**RYBELSUS\(^®\) 14 mg vs Jardiance\(^®\) 25 mg\(^1\,^5\)**  
**ADDED TO METFORMIN**  
**26-WEEK PRIMARY ENDPOINT**

### Line Graph

**Mean Change in A1C from Baseline (%)**

- **RYBELSUS\(^®\) 14 mg** (n=465; baseline: 8.4%)  
  - Baseline: 8.4%  
  - 26-week change: -1.3%  
  - **44% Greater A1C Reduction**

- **Jardiance\(^®\) 25 mg** (n=410; baseline: 8.1%)  
  - Baseline: 8.1%  
  - 26-week change: -0.9%  

**p<0.001 vs Jardiance\(^®\)**

---

**Important Safety Information**  
**Warnings and Precautions**  
- Hypoglycemia: The risk of hypoglycemia is increased when RYBELSUS\(^®\) is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Patients may require a lower dose of the secretagogue or insulin to reduce the risk of hypoglycemia in this setting.
Prescribe RYBELSUS® to a broad range of appropriate adults with type 2 diabetes

No dosage adjustment is recommended for:

- Hepatic impairment

  In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed.

- Patients aged ≥65 years

  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 (CVOT), 691 (43.4%) RYBELSUS®-treated patients were 65 years of age and over, and 196 (12.3%) 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 PK was observed.

Please see Important Safety Information regarding Acute Kidney Injury below.

Important Safety Information

- **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 with GLP-1 receptor agonists, including semaglutide. If hypersensitivity reactions occur, discontinue use of RYBELSUS®, treat promptly per standard of care, and monitor until signs and symptoms resolve. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist.

Adverse Reactions

- The most common adverse reactions, reported in ≥5% of patients treated with RYBELSUS® are nausea, abdominal pain, diarrhea, decreased appetite, vomiting and constipation.

Please see additional Important Safety Information throughout.

Please see Prescribing Information, including Boxed Warning, in the pocket.
RYBELSUS® (semaglutide) tablets 7 mg or 14 mg is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

**Use in Specific Populations**

**Drug Interactions**

Safety and tolerability evaluated across 10 Phase 3 trials.

**Severe** hypoglycemia adverse reactions are episodes requiring the assistance of another person.

Including 1 monotherapy trial and 1 trial in combination with insulin.

GI = gastrointestinal; CV = cardiovascular.

Breastfeeding and because there are alternative formulations of semaglutide that can be used during lactation, advise for medications with a narrow therapeutic index, such as levothyroxine.

**RYBELSUS® administration instructions when coadministering with other oral medications and consider increased monitoring to the long washout period for semaglutide**

Infant due to the possible accumulation of salcaprozate sodium (SNAC), an absorption enhancer in RYBELSUS®, from miscarriage, or other adverse maternal or fetal outcomes. Based on animal reproduction studies, there may be risks to the fetus.

Available data with RYBELSUS® are not sufficient to determine a drug-associated risk for major birth defects.

Safety and efficacy of RYBELSUS® have not been established in pediatric patients (younger than 18 years).

- The total number of primary component MACE endpoints was 137 respectively, due to GI adverse reactions, compared with 1% of patients receiving placebo.
- Primary endpoint was the time to first occurrence of a 3-part composite cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.
- Patients may require a lower dose of the secretagogue or insulin to effective for glycemic control.
- The 3 mg dose is intended for treatment initiation, and is not effective for glycemic control.

**STARTING DOSE**

- **3 mg**
  - Start RYBELSUS® with 3 mg once daily for 30 days

**MAINTENANCE DOSES**

- **7 mg**
  - After 30 days on the 3 mg dose, increase the dose to 7 mg once daily
- **14 mg**
  - If additional glycemic control is needed after at least 30 days on the 7 mg dose, the dose can be increased to 14 mg once daily

**ELIGIBLE PATIENTS PAY AS LITTLE AS $10 FOR A 30-DAY PRESCRIPTION**

**Two ways for your patients to get savings and support**

**Text READY to 21848**

Patients will receive co-pay savings and text messages to help them start and stay on RYBELSUS®

**Visit SAVEONR.COM**

Patients can download a savings card at SaveOnR.com and receive email support

---


Please see additional Important Safety Information throughout.

Please see Prescribing Information, including Boxed Warning, in the pocket.

RYBELSUS® is a registered trademark of Novo Nordisk A/S.
Novo Nordisk® is a registered trademark of Novo Nordisk A/S.
All other trademarks, registered or unregistered, are the property of their respective owners.
© 2019 Novo Nordisk All rights reserved. US19RYB00384 January 2020