FOR PHARMACISTS

THE WORLD'S FIRST AND ONLY ORAL GLP-1 RA

WAKE UP
TO THE POSSIBILITIES

A reference guide for pharmacists counseling adults with type 2 diabetes

GLP-1 RA=glucagon-like peptide-1 receptor agonist.

Indication 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® 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

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®**

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Please see additional Important Safety Information throughout. Please click here for Prescribing Information, including Boxed Warning.

RYBELSUS® semaglutide tablets 7mg | 14mg

To create the world's first and only oral GLP-1 RA, we had to rethink the formulation to deliver semaglutide

In order to offer patients a GLP-1 RA in a pill, we coformulated semaglutide with an absorption enhancer, which allows it to be absorbed in the stomach.[1]

Absorption enhancer locally buffers the acidic pH of the stomach, enhancing protection from degradation by gastric enzymes,[1] and

Increases transcellular absorption across the gastric epithelium[1]

Important Safety Information

Contraindications

- RYBELSUS® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2), and in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in RYBELSUS®. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with RYBELSUS®

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®

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.

  Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy

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RYBELSUS® semaglutide tablets 7mg | 14mg

Getting patients started on RYBELSUS®

Start patients on RYBELSUS® with 3 mg once daily for 30 days, then increase the dose[2]

STARTER DOSE

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

THERAPEUTIC 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

- **The 3 mg dose is intended for treatment initiation and is not effective for glycemic control**
- **Gradual dose escalation is designed to help patients adjust to their therapy**

Proper administration is important

It's important to remind your patients to take RYBELSUS® the right way, every day.

RYBELSUS® IS A ONCE-DAILY ORAL TABLET THAT MUST BE TAKEN[2]:

On an empty stomach when the patient first wakes up

With a sip of plain water (no more than 4 oz)

At least 30 minutes before the first food, beverage, or other oral medications of the day

- Waiting less than 30 minutes, or taking 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®
- If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day

Proper storage

Store tablets in the closed RYBELSUS® bottle until ready to take one[2]

Do not use a pill organizer or other container to store RYBELSUS® tablets

Swallow tablet whole.
Do not cut, crush, or chew them[2]

Important Note: The RYBELSUS® blue cap is equipped with a drying agent to help protect the tablets from moisture, which helps preserve RYBELSUS®. Tablets should be kept in the RYBELSUS® bottle with the blue cap on whenever the patient is not taking one.

Store at room temperature 68°F-77°F (20˚C-25˚C).
Store in a dry place away from moisture.

Important Safety Information

Warnings and Precautions

- **Hypoglycemia:** Patients receiving RYBELSUS® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia

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RYBELSUS® semaglutide tablets 7mg | 14mg

Prescribing Information for RYBELSUS®

Patients starting on RYBELSUS® may have received a starter kit containing a 30-day supply of the 3 mg dose along with a prescription for a 7 mg fill specifying use for at least 30 days. Once the patient has completed the pack of the 3 mg dose and the escalation to the 7 mg dose, their healthcare provider may decide to either refill the 7 mg prescription or increase their dose to 14 mg, if additional glycemic control is needed.

Trade Pack			
Strength	3 mg	7 mg	14 mg
NDC Number	0169-4303-30	0169-4307-30	0169-4314-30
Dosage Form	Tablet	Tablet	Tablet
SIG	One pill daily on an empty stomach with up to 4 oz plain water. Swallow whole. Wait 30 minutes to eat, drink, or take other oral medications.	One pill daily on an empty stomach with up to 4 oz plain water. Swallow whole. Wait 30 minutes to eat, drink, or take other oral medications.	One pill daily on an empty stomach with up to 4 oz plain water. Swallow whole. Wait 30 minutes to eat, drink, or take other oral medications.
Notes to Pharmacy	One pill daily on an empty stomach with up to 4 oz plain water. Swallow whole. Do not cut, crush, or chew. Wait 30 minutes to eat, drink, or take other oral medications.	One pill daily on an empty stomach with up to 4 oz plain water. Swallow whole. Do not cut, crush, or chew. Wait 30 minutes to eat, drink, or take other oral medications.	One pill daily on an empty stomach with up to 4 oz plain water. Swallow whole. Do not cut, crush, or chew. Wait 30 minutes to eat, drink, or take other oral medications.
Dispense Quantity	30 tablets (no refills needed for this dose)	30 tablets	30 tablets

Drug description

RYBELSUS® tablets are available as follows[2]:

Tablet Strength	Description	Package Configuration
3 mg	White to light yellow, oval-shaped, debossed with "3" on one side and "novo" on the other side	Bottle of 30 tablets
7 mg	White to light yellow, oval-shaped, debossed with "7" on one side and "novo" on the other side	Bottle of 30 tablets
14 mg	White to light yellow, oval-shaped, debossed with "14" on one side and "novo" on the other side	Bottle of 30 tablets

Help patients save on RYBELSUS®

Your eligible patients may obtain a digital savings offer via either text message or an online download.

PAY AS LITTLE AS $10 FOR A 1- TO 3-MONTH PRESCRIPTION[a]

TO GET YOUR OFFER
Text[b] **READY** to **21848** or go to **SaveOnR.com**

RYBELSUS® semaglutide tablets 7mg | 14mg

Pharmacy Connect
Helpline for the RYBELSUS® Savings Card

Call 1-888-401-0112 if you need assistance processing the RYBELSUS® Savings Card.
Available Monday through Friday, 8:00 am–8:00 pm EST

General Instructions for Pharmacists:
If you receive a rejection due to a Managed Care Restriction (eg, PA, Step Edit, or NDC Block) and the pharmacy system allows, continue processing with valid Other Coverage Code (OCC) of 03 or 08. Each pharmacy may have its own set of practice management systems and procedures. If the General Instructions do not apply, contact the RYBELSUS® Pharmacy Connect team.

NDC=National Drug Code; PA=prior authorization.

Important Safety Information

Warnings and Precautions

- **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

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Please see additional Important Safety Information throughout.
Please click here for Prescribing Information, including Boxed Warning.

Support tools for patients

Patients may ask you about support services available to them when they are taking RYBELSUS®. Included below are the different resources that are available and how patients can access them.

RYBELSUS® Connect Program
Patients can sign up for text messages with reminders, helpful information, and motivational messages! Text READY to 21848[a] to get started

RYBELSUS.com
Provides patients with more tips on incorporating RYBELSUS® into their wake-up routine, product information, and customer support

1-833-ASK-A-CDE
Offers patient one-on-one live support from a Diabetes Health Coach, if they need it. Call 1-833-ASK-A-CDE (275-2233) Monday through Friday, 9:00 am–6:00 pm ET

[a]Message and data rates may apply. Check with your mobile service provider. See Terms and Conditions of Use at RYBELSUS.com.

Visit RYBELSUSpro.com to learn more.

All RYBELSUS® support program resources are available in Spanish.

RYBELSUS® semaglutide tablets 7mg | 14mg

Frequently asked questions

Patients taking RYBELSUS® may have questions. Below are some of the questions they might ask, with helpful answers you can provide.

Why do I need to take RYBELSUS® on an empty stomach?

Taking RYBELSUS® with food, beverages (other than plain water), or other oral medications interferes with its absorption in the stomach. This will lessen its effectiveness.[2]

How strict must I be about taking RYBELSUS® with 4 oz of water?

Because of the way RYBELSUS® is absorbed, you should take it with no more than 4 oz of plain water. Anything more than that could impact the amount of RYBELSUS® that is absorbed.[2]

Can I take RYBELSUS® with just a sip of black coffee?

No. RYBELSUS® has not been studied with any beverage other than plain water. You should take RYBELSUS® with plain water only, to ensure that the medication is properly absorbed and to experience its potential benefits.[2]

Do I have to take RYBELSUS® in the morning, or at the same time every day?

For RYBELSUS® to work as intended, taking it on an empty stomach at least 30 minutes before the first food, beverage, or other oral medications of the day is what is important, which in most cases is when you first wake up.[2]

Important Safety Information

Warnings and Precautions

- **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. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist
- **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 Reactions

- Most common adverse reactions (incidence ≥5%) are nausea, abdominal pain, diarrhea, decreased appetite, vomiting and constipation

Drug Interactions

- RYBELSUS® stimulates insulin release in the presence of elevated blood glucose concentrations. When initiating RYBELSUS®, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia
- RYBELSUS® delays gastric emptying and has the potential to impact the absorption of other oral medications. Closely follow RYBELSUS® administration instructions when coadministering with other oral medications and consider increased monitoring for medications with a narrow therapeutic index, such as levothyroxine

Use in Specific Populations

- **Pregnancy:** Available data with RYBELSUS® are not sufficient to determine a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Based on animal reproduction studies, there may be risks to the fetus from exposure to RYBELSUS®. Use only if the potential benefit justifies the potential risk to the fetus

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Frequently asked questions (cont'd)

What if I miss a dose of RYBELSUS®?

If you miss a dose, the missed dose should be skipped, and the next dose should be taken the following day.[2]

Can I take more than one RYBELSUS® pill at once?

No, just take 1 pill of the prescribed dose of RYBELSUS®. As a reminder, taking two 7 mg RYBELSUS® tablets to achieve a 14 mg dose is not recommended.[2]

Can I take other pills with RYBELSUS®?

No, because of the way RYBELSUS® is absorbed, the pill is intended to sit in the stomach by itself.[1] Taking multiple pills at the same time as RYBELSUS® may impact absorption and is not recommended.[3]

How should shift workers incorporate RYBELSUS® into their routine?

Talk to your doctor and/or healthcare provider about how RYBELSUS® can be incorporated into your daily routine. People with irregular schedules may take it upon waking on an empty stomach at least 30 minutes before the first food, beverage, or other oral medications of the day, regardless of the time.[2]

Can RYBELSUS® pills be cut?

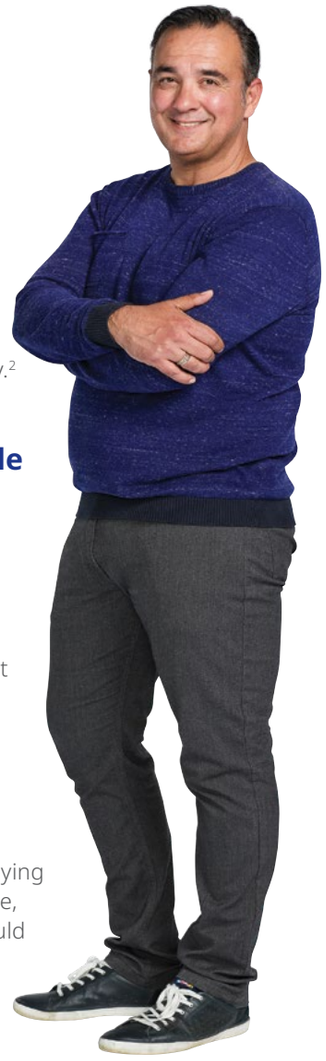
RYBELSUS® should be swallowed whole. Cutting, splitting, crushing, or chewing pills can cause the medication to not work properly.[2]

Can I remove pills from the bottle to store in pill boxes?

No. Store pills in the bottle with the blue cap on until you are ready to take them to protect tablets from moisture. Put the blue cap back on after every use. The RYBELSUS® blue cap is equipped with a drying agent to help protect the tablets from moisture, which helps preserve RYBELSUS®.[2]

Why is the blue cap significant?

The RYBELSUS® blue cap is equipped with a drying agent to help protect the tablets from moisture, which helps preserve RYBELSUS®. Tablets should be kept in the RYBELSUS® bottle with the blue cap on whenever the patient is not taking one.



Important Safety Information

Use in Specific Populations

- **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. Because of the unknown potential for serious adverse reactions in the breastfed infant due to the possible accumulation of salcaprozate sodium (SNAC), an absorption enhancer in RYBELSUS®, 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®

Important Safety Information

Use in Specific Populations

- Discontinue RYBELSUS® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide
- **Pediatric Use:** Safety and effectiveness of RYBELSUS® have not been established in pediatric patients

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In separate head-to-head studies

Superior A1C reduction vs 2 of the most-prescribed oral antidiabetic therapies, Januvia® and Jardiance®[2,4,a,b]

26-WEEK PRIMARY ENDPOINT

RYBELSUS® vs Januvia®[2,a] (*p*<0.001 for both comparisons)	RYBELSUS® vs Jardiance®[2,b] (*p*<0.001)
-1.3% with **RYBELSUS® 14 mg** (Baseline: 8.3%)	**-1.3%** with **RYBELSUS® 14 mg** (Baseline: 8.1%)
-1.0% with **RYBELSUS® 7 mg** (Baseline: 8.4%)	**-0.9%** with **Jardiance® 25 mg** (Baseline: 8.1%)
-0.8% with **Januvia® 100 mg** (Baseline: 8.3%)	

[a] **PIONEER 3: Head-to-head vs Januvia®**
In a double-blind, double-dummy trial with a primary endpoint of mean change in A1C from baseline to 26 weeks, 1864 adult 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.[2,5]

[b] **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 adult patients with type 2 diabetes on metformin were randomized to RYBELSUS® 14 mg (n=411) or Jardiance® 25 mg (n=410), both once daily.[2,6]

Common side effects with RYBELSUS®

- The most common side effects with RYBELSUS® may include nausea, stomach (abdominal) pain, diarrhea, decreased appetite, vomiting, and constipation. Nausea, vomiting, and diarrhea are most common when starting RYBELSUS®[2,c]
- If a patient experiences nausea or any other side effects while taking RYBELSUS®, advise them to talk to their healthcare provider

Here are some general nausea tips you can share with your patients that may be helpful:

- Slowly eat smaller, more frequent meals
- Eat foods that are light and bland, like saltine crackers or plain bread
- Avoid fried, greasy, or sweet foods
- Drink clear or ice-cold drinks

[c] In studies, GI side effects were more common in people taking RYBELSUS® than in people taking placebo, and people taking RYBELSUS® were more likely to stop treatment because of these side effects. Nausea, vomiting, and diarrhea may cause a loss of fluids (dehydration), which could cause existing kidney problems to get worse (including kidney failure).

GI=gastrointestinal.

No dosage adjustment recommended for[2]:

- **Patients aged ≥65 years**
  No overall differences in safety and effectiveness for RYBELSUS® have been observed between patients 65 years of age and older and younger adult patients
- **Hepatic impairment**
  In patients with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed
- **Renal impairment**
  In patients with renal impairment, including end-stage renal disease (ESRD), no clinically relevant change in semaglutide PK was observed

Important Safety Information

Warnings and Precautions

- **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

RYBELSUS®
semaglutide tablets 7mg | 14mg

RYBELSUS® IS A ONCE-DAILY ORAL TABLET THAT MUST BE TAKEN[2]:

On an empty stomach when the patient first wakes up

With a sip of plain water (no more than 4 oz)

At least 30 minutes before the first food, beverage, or other oral medications of the day

- Waiting less than 30 minutes, or taking 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®
- If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day

GETTING YOUR PATIENTS STARTED ON RYBELSUS®[2]

STARTER DOSE

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

THERAPEUTIC 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

- The 3 mg dose is intended for treatment initiation and is not effective for glycemic control
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References: 1. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Sci Transl Med.* 2018;10(467). **2.** RYBELSUS® [package insert]. Plainsboro, NJ: Novo Nordisk Inc; January 2023. **3.** Hauge C, Breitschaft A, Hartoft-Nielsen ML, Jensen S, Bækdal TA. A drug-drug interaction trial of oral semaglutide with levothyroxine and multiple co-administered tablets. Poster presented at: Endocrine Society's 101st Annual Meeting and Expo; March 23-26, 2019; New Orleans, LA., USA. **4.** IQVIA IMS Xponent TRx(SU) 4/30/2021. **5.** Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 randomized clinical trial. *JAMA.* 2019;321(15):1466-1480. **6.** Rodbard HW, Rosenstock J, Canani LH, et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. *Diabetes Care.* 2019;42(12):2272-2281.

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