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®**

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

novo nordisk®

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

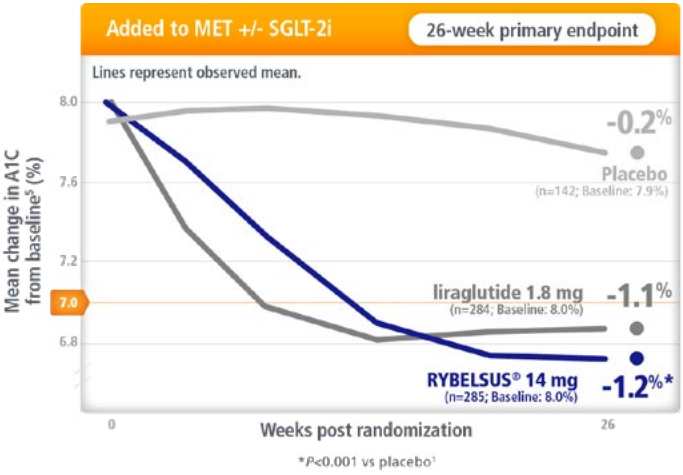
RYBELSUS®
semaglutide tablets 7mg | 14mg

Finally! A GLP-1 RA in a once-daily pill[1]

Comparable A1C reductions with RYBELSUS® 14 mg vs liraglutide 1.8 mg[1,2]

ADDED TO METFORMIN WITH OR WITHOUT SGLT-2i

26-WEEK PRIMARY ENDPOINT



*P<0.001 vs placebo[1]

Study design[1,2]

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

...with superior weight reduction with RYBELSUS® 14 mg vs liraglutide 1.8 mg and placebo[1,2]

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])

ETD=estimated treatment difference.

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

Important Safety Information

Contraindications

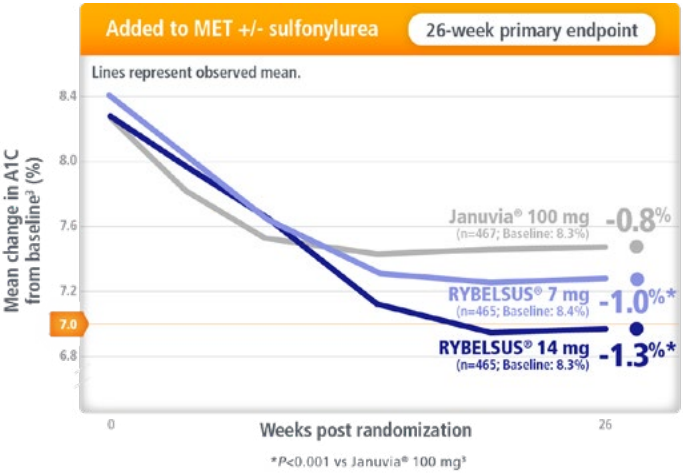
- RYBELSUS® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2), and in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in RYBELSUS®.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

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



63% GREATER A1C REDUCTION WITH 14 MG

Study design[1,4]

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 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

...with superior weight reduction with RYBELSUS® 7 mg and RYBELSUS® 14 mg vs Januvia 100 mg[1,4]

RYBELSUS® is not indicated for weight loss.

- -4.8 lb and -6.8 lb mean change in body weight from baseline to week 26 for RYBELSUS® 7 mg and RYBELSUS® 14 mg, respectively (Baseline: 201 lb for both)
- -1.3 lb mean change in body weight from baseline to week 26 for Januvia® 100 mg (Baseline: 200 lb; RYBELSUS® 7 mg ETD -3.5 lb [95% CI, -4.4, -2.4; RYBELSUS® 14 mg ETD -5.5 [95% CI, -6.6, -4.4])

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®

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

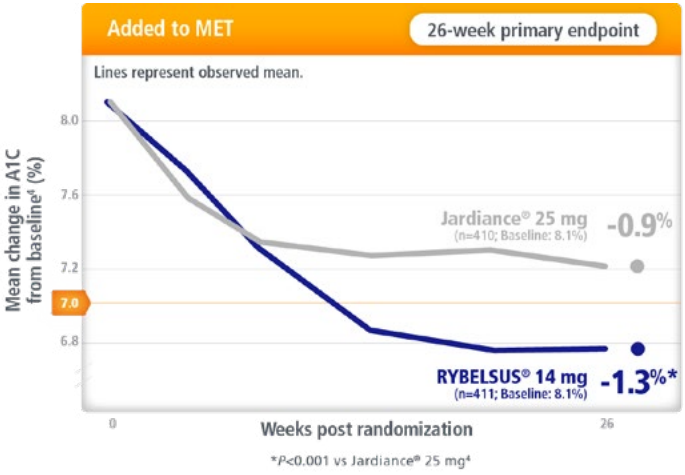
RYBELSUS® semaglutide tablets 7mg | 14mg

Superior A1C reduction vs the most prescribed[3] SGLT-2i (Jardiance®)[1]

RYBELSUS® 14 mg vs Jardiance® 25 mg[1,5]

ADDED TO METFORMIN

26-WEEK PRIMARY ENDPOINT



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

...with comparable weight reduction with RYBELSUS® 14 mg[1,5]

RYBELSUS® is not indicated for weight loss.

- -8.4 lb mean change in body weight from baseline to week 26 for RYBELSUS® 14 mg (Baseline: 202 lb)
- -8.1 lb mean change in body weight from baseline to week 26 for Jardiance® 25 mg (Baseline: 201 lb; ETD -0.2 lb [95% CI, -1.5, 1.1])

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
- **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

Prescribe RYBELSUS® to a broad range of appropriate adults with type 2 diabetes

No dosage adjustment is recommended for[1]:

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 effectiveness for RYBELSUS® have been observed between patients 65 years of age and older and younger adult patients

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/1.73m^2). 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.

eGFR=estimated glomerular filtration rate.

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
- **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

Safety and tolerability evaluated across 10 Phase 3 trials[1,6-8,a]

RATES OF GI SYMPTOMS IN PLACEBO-CONTROLLED TRIALS[1]

- The most frequently reported adverse reactions were GI disorders, including nausea, abdominal pain, and diarrhea
- Nausea, vomiting, and/or diarrhea occurred mostly during dose escalation
- 4% and 8% of patients discontinued RYBELSUS® 7 mg and 14 mg, respectively, due to GI adverse reactions, compared with 1% of patients receiving placebo

RATES OF HYPOGLYCEMIA IN PLACEBO-CONTROLLED TRIALS[1]

- Incidence of severe hypoglycemia was ≤1%[b]
- Hypoglycemia was more frequent when RYBELSUS® was used in combination with insulin secretagogues (eg, sulfonylureas) or insulin
  - Patients may require a lower dose of the secretagogue or insulin to reduce the risk of hypoglycemia in this setting

DEMONSTRATED CV SAFETY WITH NO INCREASED RISK OF MACE[1]

- A CVOT compared RYBELSUS® added to standard of care vs placebo added to standard of care
- Primary endpoint was the time to first occurrence of a 3-part composite outcome of major adverse cardiovascular events (MACEs), which included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke
- The total number of primary component MACE endpoints was 137 (61 [3.8%] with RYBELSUS® and 76 [4.8%] with placebo)

CV=cardiovascular; GI=gastrointestinal.
[a]Including 1 monotherapy trial and 1 trial in combination with insulin.[1]
[b]"Severe" hypoglycemia adverse reactions are episodes requiring the assistance of another person.[1]

Important Safety Information

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
- **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®
- 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

RYBELSUS®
semaglutide tablets 7mg | 14mg

The first type 2 diabetes pill in its class (GLP-1 RA)

Must be taken on an empty stomach when the patient first wakes up

Must be taken with a sip of plain water (no more than 4 oz)

Must be taken 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®
- Swallow whole. Do not split, crush, or chew tablets

STARTING DOSE

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

The 3 mg dose is intended for treatment initiation and is not effective for glycemic control.

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

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ELIGIBLE PATIENTS PAY AS LITTLE AS **$10 FOR A 30-, 60-, OR 90-DAY SUPPLY**[a]

Two ways for your patients to get savings and support

Text READY to 21848[b]

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

[a] Offer available only to commercially insured patients with RYBELSUS® coverage. Maximum savings of $300 per 30-day supply, $600 per 60-day supply or $900 per 90-day supply. RYBELSUS® 3 mg strength is limited to a 30-day supply only. Eligibility and restrictions apply.

[b] Message and data rates may apply. Tell patients to check with their mobile service provider. See Terms of Use & Conditions at RYBELSUS.com.

To learn more about RYBELSUS®, visit RYBELSUSpro.com

References: 1. RYBELSUS® [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; January 2023. **2.** Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet*. 2019;394(10192):39-50. **3.** IQVIA IMS Xponent TRx(SU) 12/16/22. **4.** 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. **5.** 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;42:2272-2281. **6.** Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. *Lancet Diabetes Endocrinol*. 2019;7(7):528-539. **7.** Novo Nordisk A/S. Dose-response, safety and efficacy of oral semaglutide versus placebo and versus liraglutide, all as monotherapy in Japanese subjects with type 2 diabetes (PIONEER 9). Accessed January 5, 2023. https://clinicaltrials.gov/ct2/show/NCT03018028. **8.** Novo Nordisk A/S. Safety and efficacy of oral semaglutide versus dulaglutide both in combination with one OAD (Oral Antidiabetic Drug) in Japanese subjects with type 2 diabetes (PIONEER 10). Accessed January 5, 2023. https://clinicaltrials.gov/ct2/show/NCT03015220.

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