

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RYBELSUS® safely and effectively. See full prescribing information for RYBELSUS.

RYBELSUS (semaglutide) tablets, for oral use

Initial U.S. Approval: 2017

WARNING: RISK OF THYROID C-CELL TUMORS See full prescribing information for complete boxed warning.

- In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether RYBELSUS causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).
- RYBELSUS is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).

INDICATIONS AND USAGE

RYBELSUS is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

Limitations of Use

- Has not been studied in patients with a history of pancreatitis (1, 5.2).
- Not for treatment of type 1 diabetes mellitus (1).

DOSAGE AND ADMINISTRATION

- Instruct patients to 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 with food, beverages (other than plain water) or other oral medications will lessen the effect of RYBELSUS. Waiting more than 30 minutes to eat may increase the absorption of RYBELSUS (2.1).
- Swallow tablets whole. Do not split, crush, or chew tablets (2.1).
- Start RYBELSUS with 3 mg once daily for 30 days. After 30 days on the 3 mg dosage, increase the dosage to 7 mg once daily (2.2).
- Dosage may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dosage (2.2).
- See the Full Prescribing Information for instructions on switching between OZEMPIC® and RYBELSUS (2.3).

DOSAGE FORMS AND STRENGTHS

Tablets: 3 mg, 7 mg and 14 mg (3).

CONTRAINDICATIONS

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).
- Prior serious hypersensitivity reaction to semaglutide or any of the excipients in RYBELSUS (4).

WARNINGS AND PRECAUTIONS

- **Pancreatitis:** Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- **Diabetic Retinopathy Complications:** Has been reported in a cardiovascular outcomes trial with semaglutide injection. Patients with a history of diabetic retinopathy should be monitored (5.3).
- **Hypoglycemia:** Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary (5.4).
- **Acute Kidney Injury:** Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.5).
- **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. Discontinue RYBELSUS if suspected and promptly seek medical advice (5.6).
- **Acute Gallbladder Disease:** If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.7)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 5\%$) are nausea, abdominal pain, diarrhea, decreased appetite, vomiting and constipation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc., at 1-833-457-7455 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Oral Medications: RYBELSUS delays gastric emptying. Instruct patients to closely follow RYBELSUS administration instructions (7.2).

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May cause fetal harm (8.1).
- **Lactation:** Breastfeeding not recommended (8.2).
- **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 (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2024

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FULL PRESCRIBING 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 [see *Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)*].
- RYBELSUS is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) [see *Contraindications (4)*]. 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 [see *Contraindications (4) and Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

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

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 [see *Warnings and Precautions (5.2)*].
- RYBELSUS is not indicated for use in patients with type 1 diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Instruct patients to 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 [see *Clinical Pharmacology (12.3)*]. 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.

2.2 Recommended Dosage

- Start RYBELSUS with 3 mg once daily for 30 days. The 3 mg dosage is intended for treatment initiation and is not effective for glycemic control.
- After 30 days on the 3 mg dosage, increase the dosage to 7 mg once daily.
- The dosage may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dosage.
- Taking two 7 mg RYBELSUS tablets to achieve a 14 mg dosage is not recommended.
- If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day.

2.3 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.

3 DOSAGE FORMS AND STRENGTHS

RYBELSUS tablets are available as:

- 3 mg: white to light yellow, oval shaped debossed with “3” on one side and “novo” on the other side.
- 7 mg: white to light yellow, oval shaped debossed with “7” on one side and “novo” on the other side.
- 14 mg: white to light yellow, oval shaped debossed with “14” on one side and “novo” on the other side.

4 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) [see *Warnings and Precautions (5.1)*].
- 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 [see *Warnings and Precautions (5.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 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 [see *Nonclinical Toxicology (13.1)*]. 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.

5.2 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.

5.3 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.

5.4 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 [*see Adverse Reactions (6.1) and Drug Interactions (7)*].

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.

5.5 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.

5.6 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. RYBELSUS is contraindicated in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in RYBELSUS. [*see Adverse Reactions (6.2)*].

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.

5.7 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 [*see Adverse Reactions (6.2)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors [*see Warnings and Precautions (5.1)*]
- Pancreatitis [*see Warnings and Precautions (5.2)*]

- Diabetic Retinopathy Complications [see Warnings and Precautions (5.3)]
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin [see Warnings and Precautions (5.4)]
- Acute Kidney Injury [see Warnings and Precautions (5.5)]
- Hypersensitivity [see Warnings and Precautions (5.6)]
- Acute Gallbladder Disease [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pool of Placebo-Controlled Trials

The data in Table 1 are derived from 2 placebo-controlled trials in adult patients with type 2 diabetes [see *Clinical Studies (14)*]. These data reflect exposure of 1071 patients to RYBELSUS with a mean duration of exposure of 41.8 weeks. The mean age of patients was 58 years, 3.9% were 75 years or older and 52% were male. In these trials, 63% were White, 6% were Black or African American, and 27% were Asian; 19% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 9.4 years and had a mean HbA_{1c} of 8.1%. At baseline, 20.1% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR \geq 90 mL/min/1.73m²) in 66.2%, mildly impaired (eGFR 60 to 90 mL/min/1.73m²) in 32.4% and moderately impaired (eGFR 30 to 60 mL/min/1.73m²) in 1.4% of patients.

Pool of Placebo- and Active-Controlled Trials

The occurrence of adverse reactions was also evaluated in a larger pool of adult patients with type 2 diabetes participating in 9 placebo- and active-controlled trials [see *Clinical Studies (14)*]. In this pool, 4116 patients with type 2 diabetes were treated with RYBELSUS for a mean duration of 59.8 weeks. The mean age of patients was 58 years, 5% were 75 years or older and 55% were male. In these trials, 65% were White, 6% were Black or African American, and 24% were Asian; 15% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 8.8 years and had a mean HbA_{1c} of 8.2%. At baseline, 16.6% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR \geq 90 mL/min/1.73m²) in 65.9%, mildly impaired (eGFR 60 to 90 mL/min/1.73m²) in 28.5%, and moderately impaired (eGFR 30 to 60 mL/min/1.73m²) in 5.4% of the patients.

Common Adverse Reactions

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of RYBELSUS in adult patients with type 2 diabetes in the pool of placebo-controlled trials. These adverse reactions occurred more commonly on RYBELSUS than on placebo and occurred in at least 5% of patients treated with RYBELSUS.

Table 1. Adverse Reactions in Placebo-Controlled Trials Reported in \geq 5% of RYBELSUS-Treated Patients with Type 2 Diabetes Mellitus

Adverse Reaction	Placebo (N=362) %	RYBELSUS 7 mg (N=356) %	RYBELSUS 14 mg (N=356) %
Nausea	6	11	20
Abdominal Pain	4	10	11
Diarrhea	4	9	10
Decreased appetite	1	6	9
Vomiting	3	6	8
Constipation	2	6	5

In the pool of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

Gastrointestinal Adverse Reactions

In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving RYBELSUS than placebo (placebo 21%, RYBELSUS 7 mg 32%, RYBELSUS 14 mg 41%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation. More patients receiving RYBELSUS 7 mg (4%) and RYBELSUS 14 mg (8%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (1%).

In addition to the reactions in Table 1, the following gastrointestinal adverse reactions with a frequency of <5% were associated with RYBELSUS (frequencies listed, respectively, as placebo; 7 mg; 14 mg): abdominal distension (1%, 2%, 3%), dyspepsia (0.6%, 3%, 0.6%), eructation (0%, 0.6%, 2%), flatulence (0%, 2%, 1%), gastroesophageal reflux disease (0.3%, 2%, 2%), and gastritis (0.8%, 2%, 2%).

Other Adverse Reactions

Pancreatitis

In the pool of placebo- and active-controlled trials with RYBELSUS, 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).

Diabetic Retinopathy Complications

In the pool of placebo- and active-controlled trials with RYBELSUS, patients reported diabetic retinopathy related adverse reactions during the trial (4.2% with RYBELSUS and 3.8% with comparator).

Hypoglycemia

Table 2 summarizes the incidence of hypoglycemia by various definitions in the placebo-controlled trials.

Table 2. Hypoglycemia Adverse Reactions in Placebo-Controlled Trials In Patients with Type 2 Diabetes Mellitus

	Placebo	RYBELSUS 7 mg	RYBELSUS 14 mg
Monotherapy			
(26 weeks)	N=178	N=175	N=175
Severe*	0%	1%	0%
Plasma glucose <54 mg/dL	1%	0%	0%
Add-on to metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin in patients with moderate renal impairment			
(26 weeks)	N=161	-	N=163
Severe*	0%	-	0%
Plasma glucose <54 mg/dL	3%	-	6%
Add-on to insulin with or without metformin			
(52 weeks)	N=184	N=181	N=181
Severe*	1%	0%	1%
Plasma glucose <54 mg/dL	32%	26%	30%

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

Hypoglycemia was more frequent when RYBELSUS was used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin.

Increases in Amylase and Lipase

In placebo-controlled trials, patients exposed to RYBELSUS 7 mg and 14 mg had a 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.

Cholelithiasis

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.

Increases in Heart Rate

In placebo-controlled trials, RYBELSUS 7 mg and 14 mg resulted in a mean increase in heart rate of 1 to 3 beats per minute. There was no change in heart rate in placebo-treated patients.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of semaglutide, the active ingredient of RYBELSUS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal: ileus

Hypersensitivity: anaphylaxis, angioedema, rash, urticaria

Hepatobiliary: cholecystitis, cholelithiasis requiring cholecystectomy

Nervous system disorders: dizziness, dysgeusia

7 DRUG INTERACTIONS

7.1 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

RYBELSUS stimulates insulin release in the presence of elevated blood glucose concentrations. Patients receiving RYBELSUS in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia.

When initiating RYBELSUS, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia [*see Warnings and Precautions (5.4) and Adverse Reactions (6.1)*].

7.2 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% (90% CI: 125-142) when administered with RYBELSUS in a drug interaction study [*see Clinical Pharmacology (12.3)*].

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 [*see Dosage and Administration (2)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 (*see Clinical Considerations*). 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 (*see Data*).

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an $HbA_{1c} > 7$ and has been reported to be as high as 20–25% in women with a $HbA_{1c} > 10$. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease associated maternal and fetal risk

Poorly controlled diabetes during pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

In a combined fertility and embryofetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.2-, 0.7-, and 2.1-fold the MRHD) were administered to males for 4 weeks prior to and throughout mating and to females for 2 weeks prior to mating, and throughout organogenesis to Gestation Day 17. In parental animals, pharmacologically mediated reductions in body weight gain and food consumption were observed at all dose levels. In the offspring, reduced growth and fetuses with visceral (heart blood vessels) and skeletal (cranial bones, vertebra, ribs) abnormalities were observed at the human exposure.

In an embryofetal development study in pregnant rabbits, subcutaneous doses of 0.0010, 0.0025 or 0.0075 mg/kg/day (0.06-, 0.6-, and 4.4-fold the MRHD) were administered throughout organogenesis from Gestation Day 6 to 19. Pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at ≥ 0.0025 mg/kg/day, at clinically relevant exposures.

In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (1.9-, 9.9-, and 29-fold the MRHD) were administered throughout organogenesis, from Gestation Day 16 to 50. Pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) at ≥ 0.075 mg/kg twice weekly ($\geq 9X$ human exposure).

In a pre- and postnatal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (1.3-, 6.4-, and 14-fold the MRHD) were administered from Gestation Day 16 to 140. Pharmacologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with an increase in early pregnancy losses and led to delivery of slightly smaller offspring at ≥ 0.075 mg/kg twice weekly ($\geq 6X$ human exposure).

Salcaprozate sodium (SNAC), an absorption enhancer in RYBELSUS, crosses the placenta and reaches fetal tissues in rats. In a pre- and postnatal development study in pregnant Sprague Dawley rats, SNAC was

administered orally at 1,000 mg/kg/day (exposure levels were not measured) on Gestation Day 7 through lactation day 20. An increase in gestation length, an increase in the number of stillbirths and a decrease in pup viability were observed.

8.2 Lactation

Risk Summary

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. 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.

Data

In lactating rats, semaglutide was detected in milk at levels 3-12 fold lower than in maternal plasma. SNAC and/or its metabolites were detected in milk of lactating rats following a single maternal administration on lactation day 10. Mean levels of SNAC and/or its metabolites in milk were approximately 2-12 fold higher than in maternal plasma.

8.3 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 [*see Use in Specific Populations (8.1)*].

8.4 Pediatric Use

The safety and effectiveness of RYBELSUS have not been established in pediatric patients.

8.5 Geriatric Use

In the pool of glycemic control trials, 1229 (30%) RYBELSUS-treated patients were 65 years of age and over and 199 (5%) RYBELSUS-treated patients were 75 years of age and over [*see Clinical Studies (14)*]. In PIONEER 6, the cardiovascular outcomes trial, 891 (56%) RYBELSUS-treated patients were 65 years of age and over and 200 (13%) 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.

8.6 Renal Impairment

The safety and effectiveness 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) [*see Clinical Studies (14.1)*]. In patients with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed [*see Clinical Pharmacology (12.3)*].

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

8.7 Hepatic Impairment

In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed [*see Clinical Pharmacology (12.3)*].

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

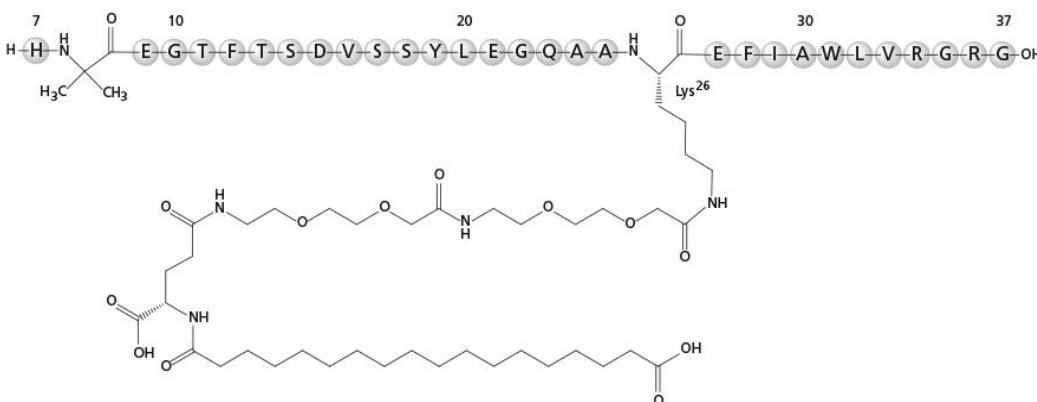
10 OVERDOSAGE

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of RYBELSUS of approximately 1 week.

11 DESCRIPTION

RYBELSUS tablets, for oral use, contain semaglutide, a GLP-1 receptor agonist. The peptide backbone is produced by yeast fermentation. The main protraction mechanism of semaglutide is albumin binding, facilitated by modification of position 26 lysine with a hydrophilic spacer and a C18 fatty di-acid. Furthermore, semaglutide is modified in position 8 to provide stabilization against degradation by the enzyme dipeptidyl-peptidase 4 (DPP-4). A minor modification was made in position 34 to ensure the attachment of only one fatty di-acid. The molecular formula is $C_{187}H_{291}N_{45}O_{59}$ and the molecular weight is 4113.58 g/mol.

Structural formula:



Semaglutide is a white to almost white hygroscopic powder. Each tablet of RYBELSUS contains 3 mg, 7 mg or 14 mg of semaglutide and the following inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone and salcaprozate sodium (SNAC).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

GLP-1 is a physiological hormone that has multiple actions on glucose, mediated by the GLP-1 receptors.

The principal mechanism of protraction resulting in the long half-life of semaglutide is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilized against degradation by the DPP-4 enzyme.

Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase.

12.2 Pharmacodynamics

All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state semaglutide injection 1 mg.

Fasting and Postprandial Glucose

Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue RYBELSUS promptly and contact their physician if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting) [see *Warnings and Precautions (5.2)*].

Diabetic Retinopathy Complications

Inform patients to contact their physician if changes in vision are experienced during treatment with RYBELSUS [see *Warnings and Precautions (5.3)*].

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Inform patients that the risk of hypoglycemia is increased when RYBELSUS is used with an insulin secretagogue (such as a sulfonylurea) or insulin. Educate patients on the signs and symptoms of hypoglycemia [see *Warnings and Precautions (5.4)*].

Dehydration and Renal Failure

Advise patients treated with RYBELSUS of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs [see *Warnings and Precautions (5.5)*].

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of RYBELSUS. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking RYBELSUS and seek medical advice promptly if such symptoms occur [see *Warnings and Precautions (5.6)*].

Acute Gallbladder Disease

Inform patients of the potential risk for cholelithiasis or cholecystitis. Instruct patients to contact their physician if cholelithiasis or cholecystitis is suspected for appropriate clinical follow-up [see *Warnings and Precautions (5.7)*].

Pregnancy

Advise a pregnant woman of the potential risk to a fetus. Advise women to inform their healthcare provider if they are pregnant or intend to become pregnant [see *Use in Specific Populations (8.1), (8.3)*].

Lactation

Advise females not to breastfeed during treatment with RYBELSUS [see *Use in Specific Populations (8.2)*].

Females and Males of Reproductive Potential

Discontinue RYBELSUS at least 2 months before a planned pregnancy due to the long washout period for semaglutide [see *Use in Specific Populations (8.3)*].

Manufactured by:

Novo Nordisk A/S
DK-2880 Bagsvaerd
Denmark

For information about RYBELSUS contact:

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Version: 6

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PATENT INFORMATION: <http://www.novonordisk-us.com/products/product-patents.html>

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Medication Guide
RYBELSUS® (reb-EL-sus)
(semaglutide)
tablets, for oral use

Read this Medication Guide before you start using RYBELSUS and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about RYBELSUS?

RYBELSUS may cause serious side effects, including:

- **Possible thyroid tumors, including cancer.** Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rodents, RYBELSUS and medicines that work like RYBELSUS caused thyroid tumors, including thyroid cancer. It is not known if RYBELSUS will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use RYBELSUS if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is RYBELSUS?

RYBELSUS is a prescription medicine used along with diet and exercise to improve blood sugar (glucose) in adults with type 2 diabetes.

- It is not known if RYBELSUS can be used in people who have had pancreatitis.
- RYBELSUS is not for use in patients with type 1 diabetes.

It is not known if RYBELSUS is safe and effective for use in children under 18 years of age.

Do not use RYBELSUS if:

- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you have had a serious allergic reaction to semaglutide or any of the ingredients in RYBELSUS. See the end of this Medication Guide for a complete list of ingredients in RYBELSUS. Symptoms of a serious allergic reaction include:
 - swelling of your face, lips, tongue or throat
 - problems breathing or swallowing
 - severe rash or itching
 - fainting or feeling dizzy
 - very rapid heartbeat

Before using RYBELSUS, tell your healthcare provider if you have any other medical conditions, including if you:

- have or have had problems with your pancreas or kidneys.
- have a history of vision problems related to your diabetes.
- are pregnant or plan to become pregnant. It is not known if RYBELSUS will harm your unborn baby. You should stop using RYBELSUS 2 months before you plan to become pregnant. Talk to your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are breastfeeding or plan to breastfeed. Breastfeeding is not recommended during treatment with RYBELSUS.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. RYBELSUS may affect the way some medicines work and some medicines may affect the way RYBELSUS works.

Before using RYBELSUS, talk to your healthcare provider about low blood sugar and how to manage it. Tell your healthcare provider if you are taking other medicines to treat diabetes, including insulin or sulfonylureas.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take RYBELSUS?

- Take RYBELSUS exactly as your healthcare provider tells you to.
- Take RYBELSUS by mouth on an empty stomach when you first wake up.
- Take RYBELSUS with a sip of plain water (no more than 4 ounces).

- Do not split, crush or chew. Swallow RYBELSUS whole.
- After 30 minutes, you can eat, drink, or take other oral medicines.
- If you miss a dose of RYBELSUS, skip the missed dose and go back to your regular schedule.

Your dose of RYBELSUS and other diabetes medicines may need to change because of:

change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, fever, trauma, infection, surgery or because of other medicines you take.

What are the possible side effects of RYBELSUS?

RYBELSUS may cause serious side effects, including:

- **See “What is the most important information I should know about RYBELSUS?”**
- **inflammation of your pancreas (pancreatitis).** Stop using RYBELSUS and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **changes in vision.** Tell your healthcare provider if you have changes in vision during treatment with RYBELSUS.
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you use RYBELSUS with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. **Signs and symptoms of low blood sugar may include:**
 - dizziness or light-headedness
 - sweating
 - confusion or drowsiness
 - headache
 - blurred vision
 - slurred speech
 - shakiness
 - fast heartbeat
 - anxiety, irritability, or mood changes
 - hunger
 - weakness
 - feeling jittery
- **kidney problems (kidney failure).** In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse. It is important for you to drink fluids to help reduce your chance of dehydration.
- **serious allergic reactions.** Stop using RYBELSUS and get medical help right away, if you have any symptoms of a serious allergic reaction including:
 - swelling of your face, lips, tongue or throat
 - problems breathing or swallowing
 - severe rash or itching
 - fainting or feeling dizzy
 - very rapid heartbeat
- **gallbladder problems.** Gallbladder problems have happened in some people who take RYBELSUS. Tell your healthcare provider right away if you get symptoms of gallbladder problems, which may include:
 - pain in your upper stomach (abdomen)
 - fever
 - yellowing of skin or eyes (jaundice)
 - clay-colored stools

The most common side effects of RYBELSUS may include nausea, stomach (abdominal) pain, diarrhea, decreased appetite, vomiting and constipation. Nausea, vomiting and diarrhea are most common when you first start RYBELSUS.

Talk to your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of RYBELSUS.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RYBELSUS?

- Store RYBELSUS at room temperature between 68°F and 77°F (20°C to 25°C).
- Store in a dry place away from moisture.
- Store tablets in the original closed RYBELSUS bottle until you are ready to take one. Do not store in any other container.
- **Keep RYBELSUS and all medicines out of the reach of children.**

General information about the safe and effective use of RYBELSUS.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use RYBELSUS for a condition for which it was not prescribed. Do not give RYBELSUS to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about RYBELSUS that is written for health professionals.

What are the ingredients in RYBELSUS?

Active Ingredient: semaglutide

Inactive Ingredients: magnesium stearate, microcrystalline cellulose, povidone and salcaprozate sodium (SNAC).

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

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PATENT Information: <http://www.novonordisk-us.com/products/product-patents.html>

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For more information, go to www.RYBELSUS.com or call 1-833-GLP-PILL.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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