

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213182Orig1s000

LABELING

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

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (1, 5.1).
- Has not been studied in patients with a history of pancreatitis (1, 5.2).
- Not indicated for use in patients with type 1 diabetes mellitus or treatment of diabetic ketoacidosis (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 cut, crush, or chew tablets (2.1).
- Start RYBELSUS with 3 mg once daily for 30 days. After 30 days on the 3 mg dose, increase the dose to 7 mg once daily (2.2).
- Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose (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).
- Known hypersensitivity to semaglutide or any of the components 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:* When RYBELSUS is used with an insulin secretagogue or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia (5.4).
- *Acute Kidney Injury:* Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.5).
- *Hypersensitivity Reactions:* Discontinue RYBELSUS if suspected and promptly seek medical advice (5.6).

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 (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. 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 (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: 01/2020

FULL PRESCRIBING INFORMATION: CONTENTS***WARNING: RISK OF THYROID C-CELL TUMORS****1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

- 2.1 Important Administration Instructions
- 2.2 Recommended Dosage
- 2.3 Switching Patients between OZEMPIC and RYBELSUS

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Risk of Thyroid C-Cell Tumors
- 5.2 Pancreatitis
- 5.3 Diabetic Retinopathy Complications
- 5.4 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin
- 5.5 Acute Kidney Injury
- 5.6 Hypersensitivity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity

7 DRUG INTERACTIONS

- 7.1 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin
- 7.2 Oral Medications

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Overview of Clinical Studies
- 14.2 Monotherapy Use of RYBELSUS in Patients with Type 2 Diabetes Mellitus
- 14.3 Combination Therapy Use of RYBELSUS in Patients with Type 2 Diabetes Mellitus
- 14.4 Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed.

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 [see *Clinical Studies (14.1)*].

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 [see *Warnings and Precautions (5.1)*].
- 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 or for the treatment of patients with diabetic ketoacidosis, as it would not be effective in these settings.

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 dose is intended for treatment initiation and is not effective for glycemic control.
- After 30 days on the 3 mg dose, increase the dose to 7 mg once daily.
- Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose.
- Taking two 7 mg RYBELSUS tablets to achieve a 14 mg dose 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)].
- Known hypersensitivity to semaglutide or to any of the components in 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

The risk of hypoglycemia is increased when RYBELSUS is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Patients may require a lower dose of the secretagogue or insulin to reduce the risk of hypoglycemia in this setting [see *Adverse Reactions (6.1)*, *Drug Interactions (7.1)*].

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 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. Do not use in patients with a previous hypersensitivity to RYBELSUS [see *Contraindications (4)*].

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.

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)*]

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 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 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 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

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 2 to 3 beats per minute. There was no change in heart rate in placebo-treated patients.

6.2 Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with RYBELSUS may develop anti-semaglutide antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to semaglutide in the studies described below cannot be directly compared with the incidence of antibodies in other studies or to other products.

Across the placebo- and active-controlled glycemic control trials with antibody measurements, 14 (0.5%) RYBELSUS-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in RYBELSUS (i.e., semaglutide). Of the 14 semaglutide-treated patients that developed semaglutide ADAs, 7 patients (0.2% of the overall population) developed antibodies cross-reacting with native GLP-1. The neutralizing activity of the antibodies is uncertain at this time.

7 DRUG INTERACTIONS

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

The risk of hypoglycemia is increased when RYBELSUS is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin [*see Warnings and Precautions (5.4)*].

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.

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 (sternbra) 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, sternbra, 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

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

8.5 Geriatric Use

In the pool of glycemic control trials, 1229 (29.9%) RYBELSUS-treated patients were 65 years of age and over and 199 (4.8%) RYBELSUS-treated patients were 75 years of age and over. In PIONEER 6, the cardiovascular outcomes trial, 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.

8.6 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) [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

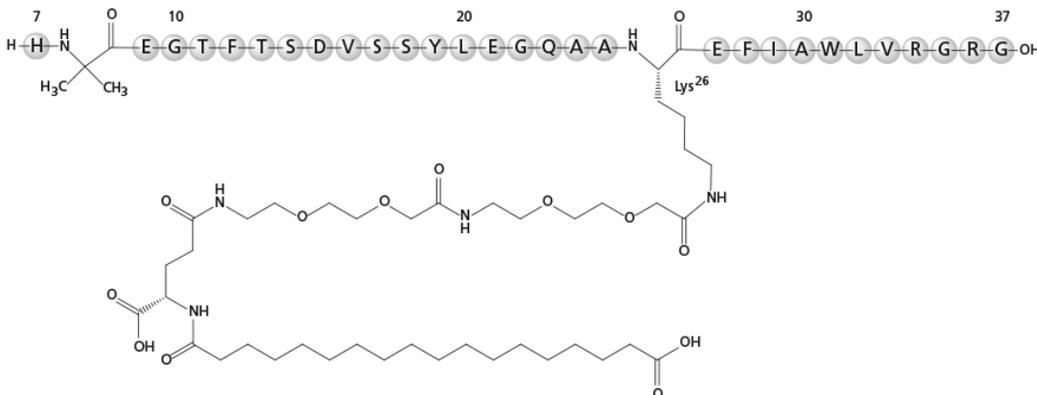
In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of RYBELSUS of approximately 1 week.

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

Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide injection 1 mg resulted in reductions in glucose in terms of absolute change from baseline and relative reduction compared to placebo of 29 mg/dL (22%) for fasting glucose, 74 mg/dL (36%) for 2 hour postprandial glucose, and 30 mg/dL (22%) for mean 24 hour glucose concentration.

Insulin Secretion

Both first- and second-phase insulin secretion are increased in patients with type 2 diabetes treated with semaglutide compared with placebo.

Glucagon Secretion

Semaglutide lowers the fasting and postprandial glucagon concentrations.

Glucose dependent insulin and glucagon secretion

Semaglutide lowers high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose-dependent manner.

During induced hypoglycemia, semaglutide did not alter the counter regulatory responses of increased glucagon compared to placebo and did not impair the decrease of C-peptide in patients with type 2 diabetes.

Gastric emptying

Semaglutide causes a delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.

Cardiac electrophysiology (QTc)

The effect of subcutaneously administered semaglutide on cardiac repolarization was tested in a thorough QTc trial. At an average exposure level 4-fold higher than that of the maximum recommended dose of RYBELSUS, semaglutide does not prolong QTc intervals to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Semaglutide is co-formulated with salcaprozate sodium which facilitates the absorption of semaglutide after oral administration. The absorption of semaglutide predominantly occurs in the stomach.

Population pharmacokinetics (PK) estimated semaglutide exposure to increase in a dose-proportional manner. In patients with type 2 diabetes, the mean population-PK estimated steady-state concentrations following once daily oral administration of 7 and 14 mg semaglutide were approximately 6.7 nmol/L and 14.6 nmol/L, respectively.

Following oral administration, maximum concentration of semaglutide is reached 1 hour post-dose. Steady-state exposure is achieved following 4-5 weeks administration.

Population-PK estimated absolute bioavailability of semaglutide to be approximately 0.4%-1%, following oral administration.

Distribution

The estimated volume of distribution of semaglutide following oral administration in healthy subjects is approximately 8 L. Semaglutide is extensively bound to plasma albumin (>99%).

Elimination

With an elimination half-life of approximately 1 week, semaglutide is present in the circulation for about 5 weeks after the last dose. The clearance of semaglutide following oral administration in healthy subjects is approximately 0.04 L/h.

Metabolism

The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain.

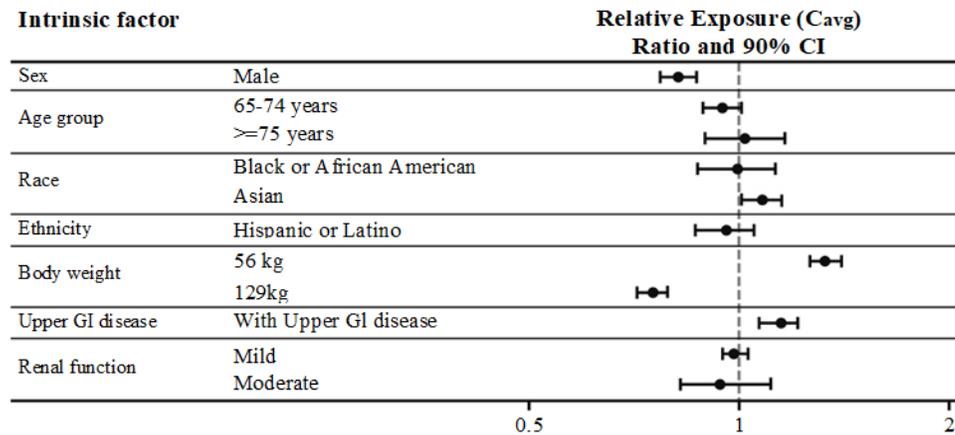
Excretion

The primary excretion routes of semaglutide-related material are via the urine and feces. Approximately 3% of the absorbed dose is excreted in the urine as intact semaglutide.

Specific Populations

Based on a population pharmacokinetic analysis, age, sex, race, ethnicity, upper GI disease, and renal impairment do not have a clinically meaningful effect on the pharmacokinetics of semaglutide. The exposure of semaglutide decreases with an increase in body weight. However, RYBELSUS doses of 7 mg and 14 mg provide adequate systemic exposure over the body weight range of 40-188 kg evaluated in the clinical trials. The effects of intrinsic factors on the pharmacokinetics of semaglutide are shown in Figure 1.

Figure 1. Impact of intrinsic factors on semaglutide exposure



Semaglutide exposure (C_{avg}) relative to reference subject profile: White, non-Hispanic or Latino female aged 18-64 years, with body weight of 85 kg, without upper GI disease or renal impairment, dosed 14 mg. Body weight categories (56 and 129 kg) represent the 5% and 95% percentiles in the dataset.

Abbreviations: C_{avg}: average semaglutide concentration. GI: gastrointestinal. CI: confidence interval.

Patients with Renal impairment - Renal impairment does not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown in a study with 10 consecutive days of once daily oral doses of semaglutide in patients with different degrees of renal impairment (mild, moderate, severe, end staged renal disease) compared with subjects with normal renal function. This was also shown for subjects with both type 2 diabetes and renal impairment based on data from clinical studies (Figure 1).

Patients with Hepatic impairment - Hepatic impairment does not have any impact on the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function in a study with 10 consecutive days of once daily oral doses of semaglutide.

Patients with disease in the upper GI tract - Upper GI disease (chronic gastritis and/or gastroesophageal reflux disease) does not impact semaglutide pharmacokinetics in a clinically relevant manner. This was shown in a study in patients with type 2 diabetes with or without upper GI disease dosed for 10 consecutive days with once daily oral doses of semaglutide.

Pediatric Patients- Semaglutide has not been studied in pediatric patients.

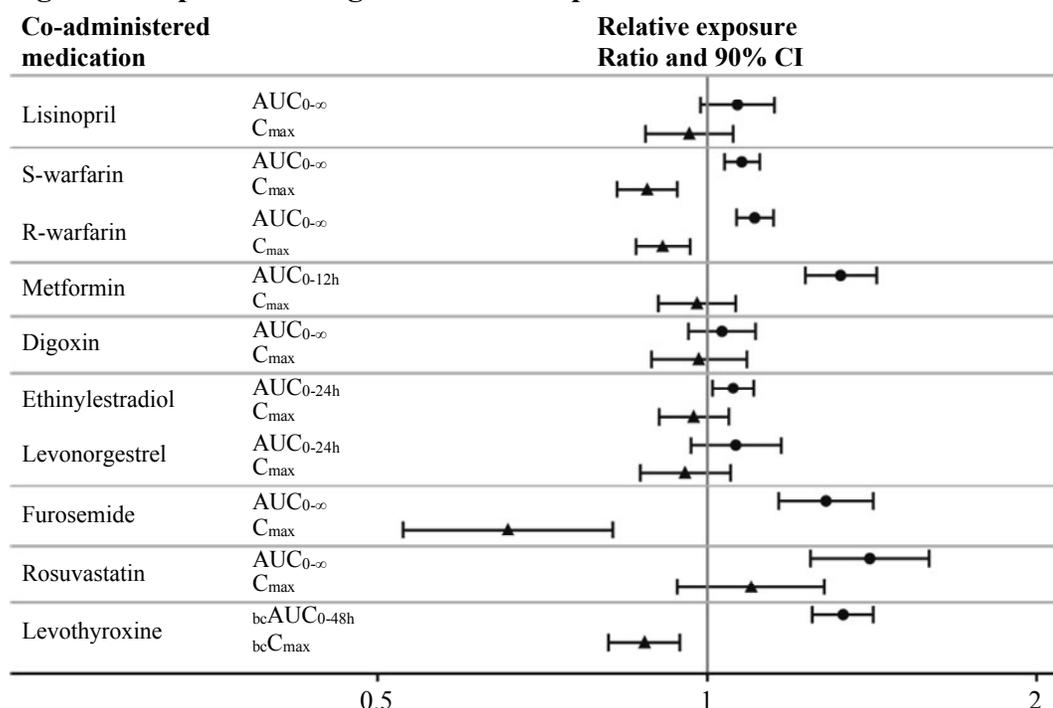
Drug Interaction Studies

In vitro studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicinal products. Trials were conducted to study the potential effect of semaglutide on the absorption of oral medications taken with semaglutide administered orally at steady-state exposure.

No clinically relevant drug-drug interaction with semaglutide (Figure 2) was observed based on the evaluated medications. Total exposure (AUC) of thyroxine (adjusted for endogenous levels) was increased by 33% following administration of a single dose of levothyroxine 600 ug concurrently administered with semaglutide. Maximum exposure (C_{max}) was unchanged [see *Drug Interactions (7.2)*].

Figure 2. Impact of semaglutide on the exposure of treatment with other oral medications



Relative exposure in terms of AUC and C_{max} for each medication when given with semaglutide compared to without semaglutide. Metformin and oral contraceptive drug (ethinylestradiol/levonorgestrel) were assessed at steady state. Effect on levothyroxine is measured as baseline corrected total T_4 (thyroxine) concentration. Lisinopril, warfarin (S-warfarin/R-warfarin), digoxin, furosemide, rosuvastatin and levothyroxine were assessed after a single dose.

Abbreviations: AUC: area under the curve. C_{max} : maximum concentration. CI: confidence interval.

No clinically relevant change in semaglutide exposure was observed when taken with omeprazole.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day [9-, 33- and 113-fold the maximum recommended human dose (MRHD) of RYBELSUS 14 mg, based on AUC] were administered to the males, and 0.1, 0.3 and 1 mg/kg/day (3-, 9-, and 33-fold MRHD) were administered to the females. A statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas were observed in males and females at all dose levels (>3X human exposure).

In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below quantification, 0.8-, 1.8- and 11-fold the exposure at the MRHD). A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all dose levels, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at ≥ 0.01 mg/kg/day, at clinically relevant exposures.

Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies [see *Boxed Warning and Warnings and Precautions (5.1)*].

Semaglutide was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial mutagenicity (Ames), human lymphocyte chromosome aberration, rat bone marrow micronucleus).

In a combined fertility and embryo-fetal 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 male and female rats. Males were dosed for 4 weeks prior to mating, and females were dosed for 2 weeks prior to mating and throughout organogenesis until Gestation Day 17. No effects were observed on male fertility. In females, an increase in estrus cycle length was observed at all dose levels, together with a small reduction in numbers of corpora lutea at ≥ 0.03 mg/kg/day. These effects were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight.

13.2 Animal Toxicology and/or Pharmacology

Increase in lactate levels and decrease in glucose levels in the plasma and cerebrospinal fluid (CSF) were observed in mechanistic studies with SNAC in rats. Small but statistically significant increases in lactate levels (up to 2-fold) were observed in a few animals at approximately the clinical exposure. At higher exposures these findings were associated with moderate to marked adverse clinical signs (lethargy, abnormal respiration, ataxia, and reduced activity, body tone and reflexes) and marked decreases in plasma and CSF glucose levels. These findings are consistent with inhibition of cellular respiration and lead to mortality at SNAC concentrations ≥ 100 -times the clinical C_{max} .

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

RYBELSUS has been studied as monotherapy and in combination with metformin, sulfonylureas, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, insulins, and thiazolidinediones in patients with type 2 diabetes. The efficacy of RYBELSUS was compared with placebo, empagliflozin, sitagliptin, and liraglutide. RYBELSUS has also been studied in patients with type 2 diabetes with mild and moderate renal impairment.

In patients with type 2 diabetes, RYBELSUS produced clinically significant reduction from baseline in HbA_{1c} compared with placebo.

The efficacy of RYBELSUS was not impacted by baseline age, gender, race, ethnicity, BMI, body weight, diabetes duration and level of renal impairment.

14.2 Monotherapy Use of RYBELSUS in Patients with Type 2 Diabetes Mellitus

In a 26-week double-blind trial (NCT02906930), 703 patients with type 2 diabetes inadequately controlled with diet and exercise were randomized to RYBELSUS 3 mg, RYBELSUS 7 mg or RYBELSUS 14 mg once daily or placebo. Patients had a mean age of 55 years and 51% were men. The mean duration of type 2 diabetes was 3.5 years, and the mean BMI was 32 kg/m². Overall, 75% were White, 5% were Black or African American, and 17% were Asian; 26% identified as Hispanic or Latino ethnicity.

Monotherapy with RYBELSUS 7 mg and RYBELSUS 14 mg once daily for 26 weeks resulted in a statistically significant reduction in HbA_{1c} compared with placebo (see Table 3).

Table 3. Results at Week 26 in a Trial of RYBELSUS as Monotherapy in Adult Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise

	Placebo	RYBELSUS 7 mg	RYBELSUS 14 mg
Intent-to-Treat (ITT) Population (N) ^a	178	175	175
HbA _{1c} (%)			
Baseline (mean)	7.9	8.0	8.0
Change at week 26 ^b	-0.3	-1.2	-1.4
Difference from placebo ^b [95% CI]		-0.9 [-1.1; -0.6] ^c	-1.1 [-1.3; -0.9] ^c
Patients (%) achieving HbA _{1c} <7%	31	69	77

FPG (mg/dL)			
Baseline (mean)	160	162	158
Change at week 26 ^b	-3	-28	-33

^aThe intent-to-treat population includes all randomized patients. At week 26, the primary HbA_{1c} endpoint was missing for 5.6%, 8.6% and 8.6% of patients randomized to placebo, RYBELSUS 7 mg and RYBELSUS 14 mg, respectively. Missing data were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. During the trial, additional anti-diabetic medication was initiated as an add on to randomized treatment by 15%, 2% and 1% of patients randomized to placebo, RYBELSUS 7 mg and RYBELSUS 14 mg, respectively.

^bEstimated using an ANCOVA model based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value and region.

^cp<0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity.

The mean baseline body weight was 88.6 kg, 89.0 kg and 88.1 kg in the placebo, RYBELSUS 7 mg, and RYBELSUS 14 mg arms, respectively. The mean changes from baseline to week 26 were -1.4 kg, -2.3 kg and -3.7 kg in the placebo, RYBELSUS 7 mg, and RYBELSUS 14 mg arms, respectively. The difference from placebo (95% CI) for RYBELSUS 7 mg was -0.9 kg (-1.9, 0.1) and for RYBELSUS 14 mg was -2.3 kg (-3.1, -1.5).

14.3 Combination Therapy Use of RYBELSUS in Patients with Type 2 Diabetes Mellitus

Combination with metformin

In a 26-week trial (NCT02863328), 822 patients with type 2 diabetes were randomized to RYBELSUS 14 mg once daily or empagliflozin 25 mg once daily, all in combination with metformin. Patients had a mean age of 58 years and 50% were men. The mean duration of type 2 diabetes was 7.4 years, and the mean BMI was 33 kg/m². Overall, 86% were White, 7% were Black or African American, and 6% were Asian; 24% identified as Hispanic or Latino ethnicity.

Treatment with RYBELSUS 14 mg once daily for 26 weeks resulted in a statistically significant reduction in HbA_{1c} compared to empagliflozin 25 mg once daily (see Table 4).

Table 4. Results at Week 26 in a Trial of RYBELSUS Compared to Empagliflozin in Adult Patients with Type 2 Diabetes Mellitus In Combination with Metformin

	RYBELSUS 14 mg	Empagliflozin 25 mg
Intent-to-Treat (ITT) Population (N) ^a	411	410
HbA _{1c} (%)		
Baseline (mean)	8.1	8.1
Change at week 26 ^b	-1.3	-0.9
Difference from empagliflozin ^b [95% CI]	-0.4 [-0.6, -0.3] ^c	
Patients (%) achieving HbA _{1c} <7%	67	40
FPG (mg/dL)		
Baseline (mean)	172	174
Change at week 26 ^b	-36	-36

^aThe intent-to-treat population includes all randomized patients. At week 26, the primary HbA_{1c} endpoint was missing for 4.6% and 3.7% of patients randomized to RYBELSUS 14 mg and empagliflozin 25 mg, respectively. Missing data were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. During the trial, additional anti-diabetic medication was initiated as an add on to randomized treatment by 1.9% and 1.2% of patients randomized to RYBELSUS 14 mg and empagliflozin 25 mg, respectively.

^bEstimated using an ANCOVA based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value and region.

^cp<0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity.

The mean baseline body weight was 91.9 kg and 91.3 kg in the RYBELSUS 14 mg and empagliflozin 25 mg arms, respectively. The mean changes from baseline to week 26 were -3.8 kg and -3.7 kg in the RYBELSUS 14

mg and empagliflozin 25 mg arms, respectively. The difference from empagliflozin (95% CI) for RYBELSUS 14 mg was -0.1 kg (-0.7, 0.5).

Combination with metformin or metformin with sulfonylurea

In a 26-week, double-blind trial (NCT02607865), 1864 patients with type 2 diabetes on metformin alone or metformin with sulfonylurea were randomized to RYBELSUS 3 mg, RYBELSUS 7 mg, RYBELSUS 14 mg or sitagliptin 100 mg once daily. Patients had a mean age of 58 years and 53% were men. The mean duration of type 2 diabetes was 8.6 years, and the mean BMI was 32 kg/m². Overall, 71% were White, 9% were Black or African American, and 13% were Asian; 17% identified as Hispanic or Latino ethnicity.

Treatment with RYBELSUS 7 mg and RYBELSUS 14 mg once daily for 26 weeks resulted in a statistically significant reduction in HbA_{1c} compared to sitagliptin 100 mg once daily (see Table 5).

Table 5. Results at Week 26 in a Trial of RYBELSUS Compared to Sitagliptin 100 mg Once daily in Adult Patients with Type 2 Diabetes Mellitus In Combination with Metformin or Metformin with Sulfonylurea

	RYBELSUS 7 mg	RYBELSUS 14 mg	Sitagliptin 100 mg
Intent-to-Treat (ITT) Population (N) ^a	465	465	467
HbA _{1c} (%)			
Baseline (mean)	8.4	8.3	8.3
Change at week 26 ^b	-1.0	-1.3	-0.8
Difference from sitagliptin ^b [95% CI]	-0.3 [-0.4; -0.1] ^c	-0.5 [-0.6; -0.4] ^c	
Patients (%) achieving HbA _{1c} <7%	44	56	32
FPG (mg/dL)			
Baseline (mean)	170	168	172
Change at week 26 ^b	-21	-31	-15

^aThe intent-to-treat population includes all randomized patients. At week 26, the primary HbA_{1c} endpoint was missing for 5.8%, 6.2% and 4.5% of patients randomized to RYBELSUS 7 mg, RYBELSUS 14 mg and sitagliptin 100 mg, respectively. Missing values were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. During the trial, additional anti-diabetic medication was initiated as an add on to randomized treatment by 2.4%, 1.1% and 2.8% of patients randomized to RYBELSUS 7 mg, RYBELSUS 14 mg and sitagliptin 100 mg, respectively.

^bEstimated using an ANCOVA based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value, background medication and region.

^cp<0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity.

The mean baseline body weight was 91.3 kg, 91.2 kg and 90.9 kg in the RYBELSUS 7 mg, RYBELSUS 14 mg and sitagliptin 100 mg arms, respectively. The mean changes from baseline to week 26 were -2.2 kg, -3.1 kg and -0.6 kg in the RYBELSUS 7 mg, RYBELSUS 14 mg and sitagliptin 100 mg arms, respectively. The difference from sitagliptin (95% CI) for RYBELSUS 7 mg was -1.6 kg (-2.0, -1.1) and RYBELSUS 14 mg was -2.5 kg (-3.0, -2.0).

Combination with metformin or metformin with SGLT-2 inhibitors

In a 26-week, double-blind, double-dummy trial (NCT02863419), 711 patients with type 2 diabetes on metformin alone or metformin with SGLT-2 inhibitors were randomized to RYBELSUS 14 mg once daily, liraglutide 1.8 mg s.c. injection once daily or placebo. Patients had a mean age of 56 years and 52% were men. The mean duration of type 2 diabetes was 7.6 years, and the mean BMI was 33 kg/m². Overall, 73% were White, 4% were Black or African American, and 13% were Asian; 6% identified as Hispanic or Latino ethnicity.

Treatment with RYBELSUS 14 mg once daily for 26 weeks resulted in statistically significant reductions in HbA_{1c} compared to placebo. Treatment with RYBELSUS 14 mg once daily for 26 weeks resulted in non-inferior reductions in HbA_{1c} compared to liraglutide 1.8 mg (see Table 6).

Table 6. Results at Week 26 in a Trial of RYBELSUS Compared to Liraglutide and Placebo in Adult Patients with Type 2 Diabetes Mellitus In Combination with Metformin or Metformin with SGLT-2i

	Placebo	Liraglutide 1.8 mg	RYBELSUS 14 mg
Intent-to-Treat (ITT) Population (N) ^a	142	284	285
HbA _{1c} (%)			
Baseline (mean)	7.9	8.0	8.0
Change at week 26 ^b	-0.2	-1.1	-1.2
Difference from placebo ^b [95% CI]			-1.1 [-1.2 ; -0.9] ^c
Difference from liraglutide ^b [95% CI]			-0.1 [-0.3; 0.0]
Patients (%) achieving HbA _{1c} <7%	14	62	68
FPG (mg/dL)			
Baseline (mean)	167	168	167
Change at week 26 ^b	-7	-34	-36

^aThe intent-to-treat population includes all randomized patients. At week 26, the primary HbA_{1c} endpoint was missing for 5.6%, 4.2% and 2.5% of patients randomized to placebo, liraglutide 1.8 mg and RYBELSUS 14 mg, respectively. Missing values were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. During the trial, additional anti-diabetic medication was initiated as an add on to randomized treatment by 7.7%, 3.2% and 3.5% of patients randomized to placebo, liraglutide 1.8 mg and RYBELSUS 14 mg respectively.

^bEstimated using an ANCOVA based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value, background medication and region.

^cp<0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity.

The mean baseline body weight was 93.2 kg, 95.5 kg and 92.9 kg in the placebo, liraglutide 1.8 mg, and RYBELSUS 14 mg arms, respectively. The mean changes from baseline to week 26 were -0.5 kg, -3.1 kg and -4.4 kg in the placebo, liraglutide 1.8 mg, and RYBELSUS 14 mg arms, respectively. The difference from placebo (95% CI) for RYBELSUS 14 mg was -3.8 kg (-4.7, -3.0). The difference from liraglutide 1.8 mg for RYBELSUS 14 mg was -1.2 (-1.9, -0.6).

Combination in patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment with Metformin alone, Sulfonylurea alone, Basal Insulin alone, or Metformin in Combination with either Sulfonylurea or Basal Insulin

In a 26-week, double-blind trial (NCT02827708), 324 patients with moderate renal impairment (eGFR_{CKD-EPI} 30–59 mL/min/1.73 m²) were randomized to RYBELSUS 14 mg or placebo once daily. RYBELSUS was added to the patient’s stable pre-trial antidiabetic regimen. The insulin dose was reduced by 20% at randomization for patients on basal insulin. Dose reduction of insulin and sulfonylurea was allowed in case of hypoglycemia; up titration of insulin was allowed but not beyond the pre-trial dose.

Patients had a mean age of 70 years and 48% were men. The mean duration of type 2 diabetes was 14 years, and the mean BMI was 32 kg/m². Overall, 96% were White, 4% were Black or African American, and 0.3% were Asian; 6.5% identified as Hispanic or Latino ethnicity. 39.5% of patients had an eGFR value of 30 to 44 mL/min/1.73 m².

Treatment with RYBELSUS 14 mg once daily for 26 weeks resulted in a statistically significant reduction in HbA_{1c} from baseline compared to placebo (see Table 7).

Table 7. Results at Week 26 in a Trial of RYBELSUS Compared to Placebo in Patients With Moderate Renal Impairment

	Placebo	RYBELSUS 14 mg
Intent-to-Treat (ITT) Population (N) ^a	161	163
HbA _{1c} (%)		
Baseline (mean)	7.9	8.0
Change at week 26 ^b	-0.2	-1.0
Difference from placebo ^b [95% CI]		-0.8 [-1.0; -0.6] ^c
Patients (%) achieving HbA _{1c} <7%	23	58
FPG (mg/dL)		
Baseline (mean)	164	164
Change at week 26 ^b	-7	-28

^aThe intent-to-treat population includes all randomized patients including patients on rescue medication. At week 26, the primary HbA_{1c} endpoint was missing for 3.7% and 5.5% of patients randomized to placebo and RYBELSUS 14 mg, respectively. Missing values were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. During the trial, additional anti-diabetic medication was initiated as an add on to randomized treatment by 10% and 4.3% of patients randomized to placebo and RYBELSUS 14 mg, respectively.

^bEstimated using an ANCOVA based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value, background medication, renal status and region.

^cp<0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity.

The mean baseline body weight was 90.4 kg and 91.3 kg in the placebo and RYBELSUS 14 mg arms, respectively. The mean changes from baseline to week 26 were -0.9 kg and -3.4 kg in the placebo and RYBELSUS 14 mg arms, respectively. The difference from placebo (95% CI) for RYBELSUS 14 mg was -2.5 kg (-3.2, -1.8).

Combination with Insulin with or without Metformin

In a 26-week double blind trial (NCT03021187), 731 patients with type 2 diabetes inadequately controlled on insulin (basal, basal/bolus or premixed) with or without metformin, were randomized to RYBELSUS 3 mg, 7 mg and 14 mg once daily or placebo once daily. All patients reduced their insulin dose by 20% at randomization to reduce the risk of hypoglycemia. Patients were allowed to increase the insulin dose only up to the starting insulin dose prior to randomization.

Patients had a mean age of 61 years and 54% were men. The mean duration of type 2 diabetes was 15 years, and the mean BMI was 31 kg/m². Overall, 51% were White, 7% were Black or African American, and 36% were Asian; 13% identified as Hispanic or Latino ethnicity.

Treatment with RYBELSUS 7 mg and 14 mg once daily for 26 weeks resulted in a statistically significant reduction in HbA_{1c} from baseline compared to placebo once daily (see Table 8).

Table 8. Results at Week 26 in a Trial of RYBELSUS Compared to Placebo in Adult Patients with Type 2 Diabetes Mellitus In Combination with Insulin alone or with Metformin

	Placebo	RYBELSUS 7 mg	RYBELSUS 14 mg
Intent-to-Treat (ITT) Population (N) ^a	184	182	181
HbA _{1c} (%)			
Baseline (mean)	8.2	8.2	8.2
Change at week 26 ^b	-0.1	-0.9	-1.3
Difference from placebo ^b		-0.9	-1.2

[95% CI]		[-1.1; -0.7] ^c	[-1.4; -1.0] ^c
Patients (%) achieving HbA _{1c} <7%	7	43	58
FPG (mg/dL)			
Baseline (mean)	150	153	150
Change at week 26 ^b	5	-20	-24

^aThe intent-to-treat population includes all randomized patients. At week 26, the primary HbA_{1c} endpoint was missing for 4.3%, 4.4%, and 4.4% of patients randomized to placebo, RYBELSUS 7 mg and RYBELSUS 14 mg, respectively. Missing values were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. During the trial, additional anti-diabetic medication was initiated as an add on to randomized treatment by 4.9%, 1.1 % and 2.2% of patients randomized to placebo, RYBELSUS 7mg and RYBELSUS 14 mg, respectively.

^bEstimated using an ANCOVA based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value, background medication and region.

^cp<0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity.

The mean baseline body weight was 86.0 kg, 87.1 kg and 84.6 kg in the placebo, RYBELSUS 7 mg, and RYBELSUS 14 mg arms, respectively. The mean changes from baseline to week 26 were -0.4 kg, -2.4 kg and -3.7 kg in the placebo, RYBELSUS 7 mg, and RYBELSUS 14 mg arms, respectively. The difference from placebo (95% CI) for RYBELSUS 7 mg was -2.0 kg (-3.0, -1.0), and for RYBELSUS 14 mg was -3.3 kg (-4.2, -2.3).

14.4 Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease

PIONEER 6 (NCT02692716) was a multi-center, multi-national, placebo-controlled, double-blind trial. In this trial, 3,183 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to RYBELSUS 14 mg once daily or placebo for a median observation time of 16 months. The trial compared the risk of a Major Adverse Cardiovascular Event (MACE) between RYBELSUS 14 mg and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and cardiovascular disease. The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

Patients eligible to enter the trial were; 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure or were 60 years of age or older and had other specified risk factors for cardiovascular disease. In total, 1,797 patients (56.5%) had established cardiovascular disease without chronic kidney disease, 354 patients (11.1%) had chronic kidney disease only, and 544 patients (17.1%) had both cardiovascular disease and kidney disease; 488 patients (15.3%) had cardiovascular risk factors without established cardiovascular disease or chronic kidney disease. The mean age at baseline was 66 years, and 68% were men. The mean duration of diabetes was 14.9 years, and mean BMI was 32 kg/m². Overall, 72% were White, 6% were Black or African American, and 20% were Asian; 16% identified as Hispanic or Latino ethnicity. Concomitant diseases of patients in this trial included, but were not limited to, heart failure (12%), history of ischemic stroke (8%) and history of a myocardial infarction (36%). In total, 99.7% of the patients completed the trial and the vital status was known at the end of the trial for 100%.

For the primary analysis, a Cox proportional hazards model was used to test for non-inferiority of RYBELSUS 14 mg to placebo for time to first MACE using a risk margin of 1.3. Type-1 error was controlled across multiple tests using a hierarchical testing strategy. Non-inferiority to placebo was established, with a hazard ratio equal to 0.79 (95% CI: 0.57, 1.11) over the median observation time of 16-months. The proportion of patients who experienced at least one MACE was 3.8% (61/1591) for RYBELSUS 14 mg and 4.8% (76/1592) for placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

RYBELSUS tablets are available as follows:

Tablet Strength	Description	Package Configuration	NDC No.
3 mg	White to light yellow, oval shaped debossed with “3” on one side and “novo” on the other side	Carton of 30 tablets (3 x 10 count blister packs)	0169-4303-13
7 mg	White to light yellow, oval shaped debossed with “7” on one side and “novo” on the other side	Carton of 30 tablets (3 x 10 count blister packs)	0169-4307-13
14 mg	White to light yellow, oval shaped debossed with “14” on one side and “novo” on the other side	Carton of 30 tablets (3 x 10 count blister packs)	0169-4314-13

Storage and Handling

Store at 68° to 77°F (20 to 25°C); excursions permitted to 59° to 86°F (15° to 30°C) [see USP Controlled Room Temperature]. Store and dispense in the original carton.

Store tablet in the original blister card until use to protect tablets from moisture. Store product in a dry place away from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Thyroid C-cell Tumors

Inform patients that semaglutide causes thyroid C-cell tumors in rodents and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician [see *Boxed Warning and Warnings and Precautions (5.1)*].

Pancreatitis

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)*].

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 to stop taking RYBELSUS and seek medical advice promptly if symptoms of hypersensitivity reactions occur [see *Warnings and Precautions (5.6)*].

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:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
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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.

- RYBELSUS is not recommended as the first choice of medicine for treating 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 and people with diabetic ketoacidosis.

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 (MEN2).
- you are allergic to semaglutide or any of the ingredients in RYBELSUS. See the end of this Medication Guide for a complete list of ingredients in RYBELSUS.

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 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 medications. RYBELSUS works best if you eat 30 to 60 minutes after taking RYBELSUS.
- If you miss a dose of RYBELSUS, skip the missed dose and go back to your regular schedule.

- Check your blood sugar as your healthcare provider tells you to.
- Stay on your prescribed diet and exercise program while using RYBELSUS.
- Talk to your healthcare provider about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your A1C.

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 itching, rash, or difficulty breathing.

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° to 25°C).
- Store in a dry place away from moisture.
- Store tablet in the original pack.
- Keep the tablet in the pack until you are ready to take it.
- **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
 RYBELSUS® is a registered trademark of Novo Nordisk A/S.
 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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/s/

LISA B YANOFF
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