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®.

ERYBELSUS® (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).

RECENT MAJOR CHANGES

Contraindications (4) ...................................................... 04/2021
Warning and Precautions, Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin (5.4) ............................. 04/2021
Warning and Precautions, Hypersensitivity (5.6) ...................... 04/2021

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 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 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).

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).

The most common adverse reactions reported in ≥5% of patients treated with RYBELSUS® and seen in ≥1% more often than with placebo are: nausea, diarrhea, weight loss, constipation, flatulence, abdominal pain, vomiting, and headache (6.1).

ADVERSE REACTIONS

6.1 Clinical Trials Experience
6.2 Immunogenicity
6.3 Postmarketing Experience

DRUG INTERACTIONS

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

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

OVERDOSAGE

10

DESCRIPTION

11

CONTRAINDICATIONS

12

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

NONCLINICAL TOXICOLOGY

13

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

CLINICAL STUDIES

14

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

HOW SUPPLIED/STORAGE AND HANDLING

16

PATIENT COUNSELING INFORMATION

17

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

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)].
• 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 is 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 ultrasonography 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 (7.2)].

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. Do not use in patients with a previous hypersensitivity to RYBELSUS® [see Contraindications (4) and Adverse Reactions (6.3)].

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.
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 56 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 or Hispanic (Hispanic/Latino). At baseline, patients had type 2 diabetes for an average of 9.4 years and had a mean HbA1c of 8.1%. At baseline, 20.1% of the population reported hypertension. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m²) in 62.2%, 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 4.1% of patients.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=362)</th>
<th>RYBELSUS® 7 mg (N=356)</th>
<th>RYBELSUS® 14 mg (N=356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>4</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

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

The increase 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 53.8 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 HbA1c of 8.2%. At baseline, 16.6% of the population reported hypertension. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m²) in 65.9%, mildly impaired (eGFR 60 to 90 mL/min/1.73m²) in 26.5%, and moderately impaired (eGFR 30 to 60 mL/min/1.73m²) in 5.4% of the patients.

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

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Placebo</th>
<th>RYBELSUS® 7 mg</th>
<th>RYBELSUS® 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>(26 weeks)</td>
<td>N=178</td>
<td>N=175</td>
<td>N=175</td>
</tr>
<tr>
<td>Severe*</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Plasma glucose &lt;54 mg/dL</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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 in 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 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.

### 6.3 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. Hypersensitivity: anaphylaxis, angioedema, rash, urticaria

### 7 DRUG INTERACTIONS

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

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)].

### 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 formation 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 HbA1c >7 and has been reported to be as high as 20–25% in women with HbA1c >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 abruptions, 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 (≥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 (≥6X human exposure).

Salcaprozae 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, 891 (58.0%) RYBELSUS®-treated patients were 65 years of age and over and 200 (12.6%) 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 (14.2)]. 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 C16H29N5O4S and the molecular weight is 411.56 ng/ml.

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.
**Figure 1. Impact of intrinsic factors on semaglutide exposure**

Intrinsic factor | Relative exposure (Cavg) | Ratio and 90% CI
--- | --- | ---
Sex | Male | 1
Age group | 65-74 years | 1
>75 years | 0.5
Race | Black or African American | 2
Asian | 1
Ethnicity | Hispanic or Latino | 1
Body weight | 56 kg | 0.5
129 kg | 2
Upper GI disease | With Upper GI disease | 1
Renal function | Mild | 1
Moderate | 2

Semaglutide exposure (Cavg) 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:** Cavg: 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 stage 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 gastro-esophageal 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 µg concurrently administered with semaglutide. Maximum exposure (Cmax) was unchanged [see Drug Interactions (7.2)].

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

<table>
<thead>
<tr>
<th>Co-administered medication</th>
<th>Relative exposure</th>
<th>Ratio and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril</td>
<td>AUC0-∞</td>
<td></td>
</tr>
<tr>
<td>R-warfarin</td>
<td>AUC0-∞</td>
<td></td>
</tr>
<tr>
<td>S-warfarin</td>
<td>AUC0-∞</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>AUC0-12h</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>AUC0-∞</td>
<td></td>
</tr>
<tr>
<td>Ethinylestradiol</td>
<td>AUC0-24h</td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>AUC0-24h</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>AUC0-∞</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>AUC0-∞</td>
<td></td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>bc AUC0-48h</td>
<td></td>
</tr>
</tbody>
</table>

Relative exposure in terms of AUC and Cmax for each medication when given with semaglutide compared to without semaglutide. Metformin and oral contraceptive drug (ethinylestradiol/levonorgestrel) were assessed at steady state. On effect on levothyroxine is measured as baseline corrected total T4 (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. Cmax: 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 Cmax.

**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 HbA1c 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
In a 26-week double-blind 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 52% 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 statistically significant reductions in HbA\(_\text{c}\) compared to empagliflozin 25 mg once daily (see Table 4).

### 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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>RYBELSUS® 7 mg</th>
<th>RYBELSUS® 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA(_\text{c}) (%)</td>
<td>7.9</td>
<td>7.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Change at week 26(^{a})</td>
<td>-0.3</td>
<td>-1.4</td>
<td>-1.4</td>
</tr>
<tr>
<td>Difference from placebo(^{b})</td>
<td>[-1.1, -0.6](^{c})</td>
<td>[-1.3, -0.9](^{c})</td>
<td></td>
</tr>
<tr>
<td>Patients (%) achieving HbA(_\text{c}) &lt;7%</td>
<td>31</td>
<td>60</td>
<td>77</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>160</td>
<td>162</td>
<td>158</td>
</tr>
<tr>
<td>Change at week 26(^{d})</td>
<td>-3</td>
<td>-28</td>
<td>-33</td>
</tr>
</tbody>
</table>

\(^{a}\)The intent-to-treat population includes all randomized patients. At week 26, the primary HbA\(_\text{c}\) endpoint was missing for 5.6%, 6.1% and 7.9% 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.

\(^{b}\)Estimated using an ANCOVA model based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value and region.

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\(_\text{c}\) 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

<table>
<thead>
<tr>
<th></th>
<th>RYBELSUS® 7 mg</th>
<th>RYBELSUS® 14 mg</th>
<th>Sitagliptin 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA(_\text{c}) (%)</td>
<td>8.4</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Change at week 26(^{a})</td>
<td>-1.0</td>
<td>-1.3</td>
<td>-0.8</td>
</tr>
<tr>
<td>Difference from sitagliptin(^{b})</td>
<td>[-0.3, -0.1]</td>
<td>[-0.6, -0.4](^{c})</td>
<td></td>
</tr>
<tr>
<td>Patients (%) achieving HbA(_\text{c}) &lt;7%</td>
<td>44</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>170</td>
<td>168</td>
<td>172</td>
</tr>
<tr>
<td>Change at week 26(^{d})</td>
<td>-21</td>
<td>-31</td>
<td>-15</td>
</tr>
</tbody>
</table>

\(^{a}\)The intent-to-treat population includes all randomized patients. At week 26, the primary HbA\(_\text{c}\) endpoint was missing for 5.6%, 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%, 1.3% and 1.4% of patients randomized to RYBELSUS® 7 mg, RYBELSUS® 14 mg and sitagliptin 100 mg, respectively.

\(^{b}\)Estimated 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.

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 7.8 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\(_\text{c}\) compared to placebo. Treatment with RYBELSUS® 14 mg once daily for 26 weeks resulted in non-inferior reductions in HbA\(_\text{c}\) 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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Liraglutide 1.8 mg</th>
<th>RYBELSUS® 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA(_\text{c}) (%)</td>
<td>7.9</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Change at week 26(^{a})</td>
<td>-0.2</td>
<td>-1.1</td>
<td>-1.2</td>
</tr>
<tr>
<td>Difference from placebo(^{b})</td>
<td>[-1.2, -0.9](^{c})</td>
<td>[-1.1, -0.9](^{c})</td>
<td></td>
</tr>
<tr>
<td>Patients (%) achieving HbA(_\text{c}) &lt;7%</td>
<td>67</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>172</td>
<td>174</td>
<td>174</td>
</tr>
</tbody>
</table>

\(^{a}\)The intent-to-treat population includes all randomized patients. At week 26, the primary HbA\(_\text{c}\) endpoint was missing for 4.8% 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.

\(^{b}\)Estimated 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.

Estimated 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.

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\(_\text{c}\) compared to sitagliptin 100 mg once daily (see Table 5).
In a 26-week, double-blind trial (NCT02827708), 324 patients with moderate renal impairment (eGFR<60 mL/min/1.73 m²) were randomized to RYBELSUS® 14 mg or placebo once daily. RYBELSUS® 14 mg 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 HbA1c 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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>RYBELSUS® 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%):</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.9</td>
</tr>
<tr>
<td>Change at week 26</td>
<td>-0.2</td>
</tr>
<tr>
<td>Difference from placebo (95% CI)</td>
<td>[0.1, -0.6]</td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c&lt;7%</td>
<td>23</td>
</tr>
<tr>
<td>FPG (mg/dL):</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>164</td>
</tr>
<tr>
<td>Change at week 26</td>
<td>-7</td>
</tr>
</tbody>
</table>

The intent-to-treat population includes all randomized patients including patients on rescue medication. At week 26, the primary HbA1c 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 randomization 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® 7 mg and RYBELSUS® 14 mg, respectively. Estimated 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. p<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. Comorbid 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 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:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
<th>Package Configuration</th>
<th>NDC No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg</td>
<td>White to light yellow, oval shaped debossed with “3” on one side and “novo” on the other side</td>
<td>Bottle of 30 tablets</td>
<td>0169-4303-30</td>
</tr>
<tr>
<td>7 mg</td>
<td>White to light yellow, oval shaped debossed with “7” on one side and “novo” on the other side</td>
<td>Bottle of 30 tablets</td>
<td>0169-4307-30</td>
</tr>
<tr>
<td>14 mg</td>
<td>White to light yellow, oval shaped debossed with “14” on one side and “novo” on the other side</td>
<td>Bottle of 30 tablets</td>
<td>0169-4314-30</td>
</tr>
</tbody>
</table>

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 bottle.

Tablet in the original bottle 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 C-cell tumors, such as a change in voice, difficulty swallowing, and nodules in the neck.

Diabetic Retinopathy Complications

Inform patients to contact their physician if changes in vision are experienced during treatment with RYBELSUS® [see Warnings and Precautions (5.5)].

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 (5.3)].
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)].

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)].
RYBELSUS® (semaglutide) tablets, for oral use

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®?

• 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.
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
• severe rash or itching
• 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 medications.
• 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
  • fast heartbeat
  • 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
  • problems breathing or swallowing
  • severe rash or itching
  • very rapid heartbeat

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).

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 04/2021

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

RYBELSUS® is a registered trademark of Novo Nordisk A/S.


For more information, go to www.RYBELSUS.com or call 1-833-GLP-PILL.
© 2021 Novo Nordisk US21RYB00187 5/2021