If cholelithiasis or cholecystitis are suspected, gallbladder studies should be performed. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.5). RYBELSUS is contraindicated in patients with a personal or family history of thyroid cancer (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 (T2DM). Limitations of Use: Has not been studied in patients with a history of pancreatitis (1, 5.2). Not for treatment of type 1 diabetes mellitus (1).

**DOSAGE AND ADMINISTRATION**

- Instruct patients to take RYBELSUS® at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only. Waiting less than 30 minutes, or taking with food, beverages (other than plain water) or other oral medications will lessen the effect of RYBELSUS®. Waiting more than 30 minutes to eat may increase the absorption of RYBELSUS® (2.1).
- Swallow tablets whole. Do not split, crush, or chew tablets (2.1).
- Start RYBELSUS® with 3 mg once daily for 30 days. After 30 days on the 3 mg dosage, increase the dosage to 7 mg once daily (2.2).
- Dosage may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dosage (2.2).
- See the Full Prescribing Information for instructions on switching between OZEMPIC® and RYBELSUS® (2.3).

**DOSAGE FORMS AND STRENGTHS**

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

**ADVERSE REACTIONS**

Most common adverse reactions (incidence ≥5%) are nausea, abdominal pain, diarrhea, decreased appetite, vomiting and constipation (6.1). To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc., at 1-833-457-7455 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

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

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: May cause fetal harm (8.1).
- Lactation: Breastfeeding not recommended (8.2).
- Females and Males of Reproductive Potential: Discontinue RYBELSUS® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 01/2024

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

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

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See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 01/2024

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- Hypoglycemia: Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary (5.4).
- Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.5).
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**USE IN SPECIFIC POPULATIONS**

- Pregnancy: May cause fetal harm (8.1).
- Lactation: Breastfeeding not recommended (8.2).
- Females and Males of Reproductive Potential: Discontinue RYBELSUS® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 01/2024
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 thyroid C-cell tumors 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® (see Contraindications (4) and Warnings and Precautions (5.1)).

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

Limitations of Use
• RYBELSUS® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis (see Warnings and Precautions (5.2)).
• RYBELSUS® is not indicated for use in patients with type 1 diabetes mellitus.

2 DOSAGE AND ADMINISTRATION
2.1 Important Administration Instructions
• Instruct patients to take RYBELSUS® at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only (see Clinical Pharmacology (12.3)). Waiting less than 30 minutes, or taking RYBELSUS® with food, beverages (other than plain water) or other oral medications will lessen the effect of RYBELSUS® by decreasing its absorption. Waiting more than 30 minutes to eat may increase the absorption of RYBELSUS®.
• Swallow tablets whole. Do not split, crush, or chew tablets.

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

2.3 Switching Patients between OZEMPIC® and RYBELSUS®
• Patients treated with OZEMPIC® 14 mg daily can be switched 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 tiraglutide, 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 (1.6%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (semaglutide injection 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (semaglutide injection 0.7%, placebo 0.4%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

5.4 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin
Patients receiving RYBELSUS® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia (see Adverse Reactions (6.1) and Drug Interactions (7)).

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

5.5 Acute Kidney Injury
There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists, including semaglutide. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of RYBELSUS® in patients reporting severe adverse gastrointestinal reactions.

5.6 Hypersensitivity
Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with RYBELSUS®. If hypersensitivity reactions occur, discontinue use of RYBELSUS®, treat promptly per standard of care, and monitor until signs and symptoms resolve. RYBELSUS® is contraindicated in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in RYBELSUS®. (see Adverse Reactions (6.2)).

Anaphylaxis and angioedema have been reported with GLP-1 receptor agonists. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with RYBELSUS®.

5.7 Acute Gallbladder Disease
Acute events of gallbladder disease such as cholecithiasis or cholecystitis have been reported in patients treated with GLP-1 receptor agonists and RYBELSUS®. If cholecithiasis reactions occur, discontinue use of RYBELSUS®; treat promptly per standard of care, and monitor until signs and symptoms resolve. RYBELSUS® is contraindicated in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in RYBELSUS®. (see Adverse Reactions (6.2)).

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

• Risk of Thyroid C-cell Tumors (see Warnings and Precautions (5.1))
• Pancreatitis (see Warnings and Precautions (5.2))
• Diabetic Retinopathy Complications (see Warnings and Precautions (5.3))
• Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin (see Warnings and Precautions (5.4))
• Acute Kidney Injury (see Warnings and Precautions (5.5))
• Hypersensitivity (see Warnings and Precautions (5.6))
• Acute Gallbladder Disease (see Warnings and Precautions (5.7))
6.1 Clinical Trials Experience

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

Pool of Placebo-Controlled Trials

The data in Table 1 are derived from 2 placebo-controlled trials in adult patients with type 2 diabetes [see Clinical Studies (14)]. These data reflect exposure of 1071 patients to RYBELSUS® with a mean duration of exposure of 41.8 weeks. The mean age of patients was 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; 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 HbA1c of 8.1%. At baseline, 20.1% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m²) in 66.2%, 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.

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>5</td>
<td>8</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>6</td>
<td>8</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

In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving RYBELSUS® than placebo (21.2%, 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%, 0.3%, 0.6%), eructation (0%, 0.6%, 2%), flatulence (0%, 2%, 1%), gastroesophageal reflux disease (0.3%, 2%, 2%), and gastritis (0.6%, 2%, 2%).

Other Adverse Reactions

Pancreatitis

In the pool of placebo- and active-controlled trials with RYBELSUS®, pancreatitis was reported as a serious adverse event in 6 RYBELSUS®-treated patients (0.1 events per 100 patient years) versus 1 in comparator-treated patients (<0.1 events per 100 patient years).

Diabetic Retinopathy Complications

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

Hypoglycemia

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

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

<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>

‡ 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 Postmarketing Experience

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

Gastrointestinal: ileus

Hypersensitivity: anaphylaxis, angioedema, rash, urticaria

Hepatobiliary: cholecytitis, cholelithiasis requiring cholecystectomy

Nervous system disorders: dizziness, dysgeusia

7 DRUG INTERACTIONS

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

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

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

7.2 Oral Medications

RYBELSUS® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of other oral medications. Levothyroxine exposure was increased 33% (90% CI: 125-142) when administered with RYBELSUS® in a drug interaction study [see Clinical Pharmacology (12.3)].

When coadministering oral medications instruct patients to closely follow RYBELSUS® administration instructions. Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic index or that require clinical monitoring [see Dosage and Administration (2)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with RYBELSUS® use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy [see Clinical Considerations]. Based on animal reproduction studies, there may be potential risks to the fetus from exposure to RYBELSUS® during pregnancy. RYBELSUS® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities, and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses and structural abnormalities were observed at exposure below the MRHD (rabbit) and ≥10-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species [see Data].

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to be as high as 20–25% in women with an HbA1c
RYBELSUS® (semaglutide) tablets, for oral use

>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 through 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 ≥10-fold the MRHD.

In an embryofetal development study in pregnant rabbits, subcutaneous doses of 0.0100, 0.0025 or 0.00075 mg/kg/day (0.06-, 0.6-, and 4.4-fold the MRHD) were administered throughout organogenesis, from Gestation Day 16 to 19. Pharmacologically mediated reductions in maternal body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternbra, ribs) at ≥0.075 mg/kg twice weekly (≥5X human exposure).

In an embryofetal 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 (≥5X human exposure).

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

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 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 C63H92N4O35 and the molecular weight is 4131.56 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.
Semaglutide is co-formulated with salcaprane 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 mg 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.

**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**

<table>
<thead>
<tr>
<th>Intrinsic factor</th>
<th>Relative exposure (Cavg)</th>
<th>Ratio and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;75 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>56 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>129 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper GI Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With Upper GI disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 5th and 95th percentiles in the dataset.

**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.

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**12.3 Pharmacokinetics**

**Absorption**

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](7.7)).

**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 ratio and 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-12h&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Cmax</td>
<td></td>
</tr>
<tr>
<td>S-warfarin</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-12h&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Cmax</td>
<td></td>
</tr>
<tr>
<td>R-warfarin</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-12h&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Cmax</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-12h&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Cmax</td>
<td></td>
</tr>
<tr>
<td>Metformin and contraceptive drug (ethinylestradiol/levonorgestrel) were assessed at steady state. Effect on levothyroxine is measured as baseline corrected total T&lt;sub&gt;4&lt;/sub&gt; (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.</td>
<td></td>
</tr>
<tr>
<td>No clinically relevant change in semaglutide exposure was observed when taken with omeprazole.</td>
<td></td>
</tr>
</tbody>
</table>
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, insulin, and thiazolidinediones in patients with type 2 diabetes. The efficiency of RYBELSUS® was compared with placebo, empagliflozin, sitagliptin, and lixisenatide. RYBELSUS® has also been studied in patients with type 2 diabetes in 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 adult 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 HbA1c 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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>RYBELSUS® 7 mg</th>
<th>RYBELSUS® 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Change at week 26</td>
<td>-0.3</td>
<td>-1.2</td>
</tr>
<tr>
<td>Difference from placebo</td>
<td>-0.9</td>
<td>[-1.1, -0.6]</td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c ≤7%</td>
<td>31</td>
<td>69</td>
</tr>
</tbody>
</table>

The mean baseline body weight was 88.6 kg, 88.0 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 (NCT02863419), 1864 adult 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.

Combination with Metformin or Metformin with Sulfonylureas

In a 26-week, double-blind trial (NCT02863419), 1864 adult 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 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, 7% were Black or African American, and 17% were Asian; 26% identified as Hispanic or Latino ethnicity.

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

<table>
<thead>
<tr>
<th>RYBELSUS® 14 mg</th>
<th>Empagliflozin 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treat (ITT) Population (N)</td>
<td>411</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.1</td>
</tr>
<tr>
<td>Change at week 26</td>
<td>-1.3</td>
</tr>
<tr>
<td>Difference from empagliflozin</td>
<td>-0.4</td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c ≤7%</td>
<td>67</td>
</tr>
</tbody>
</table>

The intent-to-treat population includes all randomized patients. At week 26, the primary HbA1c 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.

14.4 Monotherapy Use of RYBELSUS® in Patients with Type 2 Diabetes Mellitus

In a 26-week double-blind trial (NCT02863419), 711 adult patients with type 2 diabetes on metformin alone or metformin with SGLT-2 inhibitors were randomized to RYBELSUS® 3 mg, RYBELSUS® 7 mg and RYBELSUS® 14 mg once daily for 26 weeks. 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.

Combination with Metformin or Metformin with SGLT-2 Inhibitors

In a 26-week, double-blind, double-dummy trial (NCT02863419), 711 adult patients with type 2 diabetes on metformin alone or metformin with SGLT-2 inhibitors were randomized to RYBELSUS® 3 mg, RYBELSUS® 7 mg and RYBELSUS® 14 mg once daily for 26 weeks. 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 a statistically significant reduction in HbA1c compared to placebo. Treatment with RYBELSUS® 14 mg once daily for 26 weeks resulted in non-inferior reductions in HbA1c compared to lixisenatide 1.8 mg (see Table 6).
In a 26-week, double-blind trial (NCT02827708), 324 adult patients with moderate renal impairment (eGFR <60 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 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>6.3</td>
</tr>
<tr>
<td>Change at week 26</td>
<td>-0.4</td>
</tr>
</tbody>
</table>

*The intent-to-treat population includes all randomized patients. At week 26, the primary HbA1c endpoint was missing for 6.1% of patients in the placebo and RYBELSUS® 14 mg arms, 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%, 2% and 5% of patients randomized to placebo, liraglutide 1.8 mg and RYBELSUS® 14 mg, respectively. The difference from placebo (95% CI) for RYBELSUS® 14 mg was -0.5 kg (-1.1, -0.0). The difference from placebo (95% CI) for RYBELSUS® 14 mg was -1.2 kg (-1.9, -0.6).

*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, -0.3 kg and -0.1 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 -0.4 kg (-1.1, -0.0).

*The patients achieving HbA1c <7% were 14% in the placebo arm, 62% in the liraglutide 1.8 mg arm, and 68% in the RYBELSUS® 14 mg arm.

*The patients achieving HbA1c <7% were 7% in the placebo arm, 43% in the liraglutide 1.8 mg arm, and 58% in the RYBELSUS® 14 mg arm.

*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® 14 mg was -2.0 kg (-3.0, -1.0). The difference from placebo (95% CI) for RYBELSUS® 14 mg was -3.3 kg (-4.2, -2.3).

### 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>Placebo</th>
<th>Liraglutide 1.8 mg</th>
<th>RYBELSUS® 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>6.3</td>
<td>6.0</td>
</tr>
<tr>
<td>Change at week 26</td>
<td>-0.4</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

*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).

### 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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>RYBELSUS® 7 mg</th>
<th>RYBELSUS® 14 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>6.3</td>
<td>6.0</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Change at week 26</td>
<td>-0.1</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

*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).
16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

RYBELSUS® tablets are available as follows:

<table>
<thead>
<tr>
<th>Tablet 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>

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 bottle. Store 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

Advising 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

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

Diabetic Retinopathy Complications

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

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

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

Dehydration and Renal Failure

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

Hypersensitivity Reactions

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

Acute Gallbladder Disease

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

Pregnancy

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

Lactation

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

Females and Males of Reproductive Potential

Discontinue RYBELSUS® at least 2 months before a planned pregnancy due to the long washout period for semaglutide [see Use in Specific Populations (8.3)].
What is the most important information I should know about RYBELSUS®?

RYBELSUS® may cause serious side effects, including:

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

What is RYBELSUS®?

RYBELSUS® is a prescription medicine used along with diet and exercise to improve blood sugar (glucose) in adults with type 2 diabetes.
- It is not known if RYBELSUS® can be used in people who have had pancreatitis.
- RYBELSUS® is not for use in patients with type 1 diabetes.
- It is not known if RYBELSUS® is safe and effective for use in children under 18 years of age.

Do not use RYBELSUS® if:

- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you have had a serious allergic reaction to semaglutide or any of the ingredients in RYBELSUS®. See the end of this Medication Guide for a complete list of ingredients in RYBELSUS®.

Symptoms of a serious allergic reaction include:
- swelling of your face, lips, tongue or throat
- 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.
- are breastfeeding or plan to breastfeed. Breastfeeding is not recommended during treatment with RYBELSUS®.

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

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

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

How should I take RYBELSUS®?

- Take RYBELSUS® exactly as your healthcare provider tells you to.
- Take RYBELSUS® by mouth on an empty stomach when you first wake up.
- Take RYBELSUS® with a sip of plain water (no more than 4 ounces).
- Do not split, crush or chew. Swallow RYBELSUS® whole.
- After 30 minutes, you can eat, drink, or take other oral medicines.
- If you miss a dose of RYBELSUS®, skip the missed dose and go back to your regular schedule.

Your dose of RYBELSUS® and other diabetes medicines may need to change because of:
- change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, fever, trauma, infection, surgery or because of other medicines you take.

What are the possible side effects of RYBELSUS®?

RYBELSUS® may cause serious side effects, including:

- See “What is the most important information I should know about RYBELSUS®?”
- Inflammation of your pancreas (pancreatitis). Stop using RYBELSUS® and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- Changes in vision. Tell your healthcare provider if you have changes in vision during treatment with RYBELSUS®.
- Low blood sugar (hypoglycemia). Your risk for getting low blood sugar may be higher if you use RYBELSUS® with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. Signs and symptoms of low blood sugar may include:
  - Dizziness or light-headedness
  - Sweating
  - Confusion or drowsiness
  - Headache
  - Fast heartbeat
  - Feeling jittery
- Kidney problems (kidney failure). In people who have kidney problems, diabetes, 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
  - Severe rash or itching
  - Very rapid heartbeat
- Gallbladder problems. Gallbladder problems have happened in some people who take RYBELSUS®. Tell your healthcare provider right away if you get symptoms of gallbladder problems, which may include:
  - Pain in your upper stomach (abdomen)
  - Yellowing of skin or eyes (jaundice)
  - Clay-colored stools

The most common side effects of RYBELSUS® may include:
- Nausea, vomiting and diarrhea are common side effects of RYBELSUS®. The most common side effects of RYBELSUS® may include:
  - Nausea
  - Vomiting
  - Diarrhea
  - Decreased appetite

The most common side effects of RYBELSUS® are:
- Nausea
- Vomiting
- Diarrhea
- Decreased appetite

These are not all the possible side effects of RYBELSUS®.

Tell 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.

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Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark
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For more information, go to www.RYBELSUS.com or call 1-833-GLP-PILL.
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