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

RYBELSUS (semaglutide) tablets, for oral use
Initial U.S. Approval: 2017

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

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

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

Limitations of Use
- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (1, 5.1).
- Has not been studied in patients with a history of pancreatitis (1, 5.2).
- Not indicated for use in patients with type 1 diabetes mellitus or treatment of diabetic ketoacidosis (1).

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

·····DOSAGE FORMS AND STRENGTHS·····
Tablets: 3 mg, 7 mg and 14 mg (3).

·····CONTRAINDICATIONS·····
- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).
- Known hypersensitivity to semaglutide or any of the components in RYBELSUS (4).

·····WARNINGS AND PRECAUTIONS·····
- *Pancreatitis*: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- *Diabetic Retinopathy Complications*: Has been reported in a cardiovascular outcomes trial with semaglutide injection. Patients with a history of diabetic retinopathy should be monitored (5.3).
- *Hypoglycemia*: When RYBELSUS is used with an insulin secretagogue or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia (5.4).
- *Acute Kidney Injury*: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.5).
- *Hypersensitivity Reactions*: Discontinue RYBELSUS if suspected and promptly seek medical advice (5.6).

·····ADVERSE REACTIONS·····
The most common adverse reactions, reported in ≥5% of patients treated with RYBELSUS are: nausea, abdominal pain, diarrhea, decreased appetite, vomiting and constipation (6.1).

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

----------DRUG INTERACTIONS----------
Oral Medications: RYBELSUS delays gastric emptying. When coadministering oral medications instruct patients to closely follow RYBELSUS administration instructions. Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic index or that require clinical monitoring (7.2).

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2020

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: RISK OF THYROID C-CELL TUMORS

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether RYBELSUS causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **RYBELSUS is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Contraindications (4)]*. Counsel patients regarding the potential risk for MTC with the use of RYBELSUS and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with RYBELSUS *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

RYBELSUS is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14.1)]*.

Limitations of Use

- RYBELSUS is not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans *[see Warnings and Precautions (5.1)]*.
- RYBELSUS has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis *[see Warnings and Precautions (5.2)]*.
- RYBELSUS is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

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

2.2 Recommended Dosage

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

2.3 Switching Patients between OZEMPIC and RYBELSUS

- Patients treated with RYBELSUS 14 mg daily can be transitioned to OZEMPIC subcutaneous injection

- Patients treated with once weekly OZEMPIC 0.5 mg subcutaneous injection can be transitioned to RYBELSUS 7 mg or 14 mg. Patients can start RYBELSUS up to 7 days after their last injection of OZEMPIC. There is no equivalent dose of RYBELSUS for OZEMPIC 1 mg.

3 DOSAGE FORMS AND STRENGTHS

RYBELSUS tablets are available as:

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

4 CONTRAINDICATIONS

RYBELSUS is contraindicated in patients with:

- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Warnings and Precautions (5.1)]*.
- Known hypersensitivity to semaglutide or to any of the components in RYBELSUS *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors

In mice and rats, semaglutide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures *[see Nonclinical Toxicology (13.1)]*. It is unknown whether RYBELSUS causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

RYBELSUS is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of RYBELSUS and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with RYBELSUS. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Pancreatitis

In glycemic control trials, pancreatitis was reported as a serious adverse event in 6 RYBELSUS-treated patients (0.1 events per 100 patient years) versus 1 in comparator-treated patients (<0.1 events per 100 patient years).

After initiation of RYBELSUS, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, RYBELSUS should be discontinued and appropriate management

5.3 Diabetic Retinopathy Complications

In a pooled analysis of glycemic control trials with RYBELSUS, patients reported diabetic retinopathy related adverse reactions during the trial (4.2% with RYBELSUS and 3.8% with comparator).

In a 2-year cardiovascular outcomes trial with semaglutide injection involving patients with type 2 diabetes and high cardiovascular risk, diabetic retinopathy complications (which was a 4 component adjudicated endpoint) occurred in patients treated with semaglutide injection (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (semaglutide injection 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (semaglutide injection 0.7%, placebo 0.4%).

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

5.4 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

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

5.5 Acute Kidney Injury

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

5.6 Hypersensitivity

Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with GLP-1 receptor agonists, including semaglutide. If hypersensitivity reactions occur, discontinue use of RYBELSUS; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to RYBELSUS *[see Contraindications (4)]*.

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

6 ADVERSE REACTIONS

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

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Diabetic Retinopathy Complications *[see Warnings and Precautions (5.3)]*
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin *[see Warnings and Precautions (5.4)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.5)]*
- Hypersensitivity *[see Warnings and Precautions (5.6)]*

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