Important Safety Information for Ozempic® (semaglutide) injection

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 Ozempic® 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.**
- **Ozempic® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Ozempic® and inform them of symptoms of thyroid tumors (eg, 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 Ozempic®.**

Indications and Limitations of Use

Ozempic® (semaglutide) injection 0.5 mg, 1 mg, or 2 mg is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular (CV) events (CV death, nonfatal myocardial infarction, or nonfatal stroke) in adults with type 2 diabetes mellitus and established CV disease.

- Ozempic® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Ozempic® is not indicated for use in patients with type 1 diabetes mellitus.

Important Safety Information cont.

Contraindications

- Ozempic® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2, and in patients with a hypersensitivity reaction to semaglutide or to any of the excipients in Ozempic®. Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with Ozempic®.

Warnings and Precautions

- **Risk of Thyroid C-Cell Tumors:** Patients should be referred to an endocrinologist for further evaluation if serum calcitonin is measured and found to be elevated or thyroid nodules are noted on physical examination or neck imaging.
- **Pancreatitis:** Acute and chronic pancreatitis have been reported in clinical studies. Observe patients carefully for signs and symptoms of pancreatitis (persistent severe abdominal pain, sometimes radiating to the back with or without vomiting). If pancreatitis is suspected, discontinue Ozempic® promptly, and if pancreatitis is confirmed, do not restart.
- **Diabetic Retinopathy Complications:** In a 2-year trial involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in patients treated with Ozempic® (3.0%) compared with placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline than among patients without a known history of diabetic retinopathy.

  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.
- **Never Share an Ozempic® Pen Between Patients:** Ozempic® pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.
- **Hypoglycemia:** Patients receiving Ozempic® in combination with an insulin secretagogue (eg, sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.
- **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. 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 Ozempic® in patients reporting severe adverse gastrointestinal reactions.
- **Hypersensitivity:** Serious hypersensitivity reactions (eg, anaphylaxis, angioedema) have been reported in patients treated with Ozempic®. If hypersensitivity reactions occur, discontinue use of Ozempic®; treat promptly per standard of care, and monitor until signs

and symptoms resolve. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist.

- **Acute Gallbladder Disease:** Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients treated with Ozempic® 0.5 mg and 1 mg, respectively, and not reported in placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

Adverse Reactions

- The most common adverse reactions, reported in ≥5% of patients treated with Ozempic® are nausea, vomiting, diarrhea, abdominal pain, and constipation.

Drug Interactions

- When initiating Ozempic®, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.
- Ozempic causes a delay of gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications, so caution should be exercised.

Use in Specific Populations

- There is limited data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. Discontinue Ozempic® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

Please click here for Ozempic® Prescribing Information, including Boxed Warning.

Important Safety Information for RYBELSUS® (semaglutide) tablets 7 mg or 14 mg

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**
- **RYBELSUS® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (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®**

Indication and Usage

RYBELSUS® (semaglutide) tablets 7 mg or 14 mg is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

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
- RYBELSUS® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis
- RYBELSUS® is not indicated for use in patients with type 1 diabetes

Important Safety Information (cont'd)

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), and in patients with 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®

Warnings and Precautions

- **Risk of Thyroid C-Cell Tumors:** Patients should be further evaluated if serum calcitonin is measured and found to be elevated or thyroid nodules are noted on physical examination or neck imaging
- **Pancreatitis:** Has been reported in clinical trials. 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, discontinue RYBELSUS® and initiate appropriate management; if confirmed, do not restart RYBELSUS®
- **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 trial with semaglutide injection involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications 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 than among patients without a known history of diabetic retinopathy.

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy

- **Hypoglycemia:** Patients receiving RYBELSUS® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia
- **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
- **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. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist
- **Acute Gallbladder Disease:** Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In placebo-controlled trials, cholelithiasis was reported in 1% of patients treated with RYBELSUS® 7 mg. Cholelithiasis was not reported in RYBELSUS® 14 mg or placebo-treated patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated

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

Drug Interactions

- When initiating RYBELSUS®, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia
- RYBELSUS® delays gastric emptying and has the potential to impact the absorption of other oral medications. Closely follow RYBELSUS® administration instructions when

coadministering with other oral medications and consider increased monitoring for medications with a narrow therapeutic index, such as levothyroxine

Use in Specific Populations

- **Pregnancy:** Available data with RYBELSUS® are not sufficient to determine a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Based on animal reproduction studies, there may be risks to the fetus from exposure to RYBELSUS®. Use only if the potential benefit justifies the potential risk to the fetus
- **Lactation:** There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the unknown potential for serious adverse reactions in the breastfed infant due to the possible accumulation of salcaprozate sodium (SNAC), an absorption enhancer in RYBELSUS®, 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®
- Discontinue RYBELSUS® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide
- **Pediatric Use:** Safety and efficacy of RYBELSUS® have not been established in pediatric patients (younger than 18 years)

Please click here for Prescribing Information, including Boxed Warning.

Indications and Usage for Fiasp® (insulin aspart injection) 100 U/mL

Fiasp® (insulin aspart injection) 100 U/mL is a rapid-acting insulin analog indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus.

Important Safety Information

Contraindications

- Fiasp® is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Fiasp® or one of its excipients.

Warnings and Precautions

- **Never share a Fiasp® FlexTouch® Pen, PenFill® cartridge or PenFill® cartridge device between patients, even if the needle is changed.** Patients using Fiasp® vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

- **Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen:** Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia. Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. Adjustments in concomitant anti-diabetic treatment may be needed.
- Hypoglycemia is the most common adverse reaction of insulin, including Fiasp®, and may be life-threatening. Increase glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness.
- To avoid medication errors and accidental mix-ups between Fiasp® and other insulin products, instruct patients to always check the insulin label before injection.
- As with all insulins, Fiasp® use can lead to life-threatening hypokalemia, which then may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated.
- Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with insulin products, including Fiasp®.
- Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including Fiasp®. Patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of the TZD must be considered.
- Pump or infusion set malfunctions can lead to a rapid onset of hyperglycemia and ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection of Fiasp® may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

Adverse Reactions

- Adverse reactions observed with Fiasp® include hypoglycemia, allergic reactions, hypersensitivity, injection site reactions, lipodystrophy, and weight gain.

Use in Specific Populations

- Pediatric patients with type 1 diabetes treated with mealtime and postmeal Fiasp® reported a higher rate of blood glucose confirmed hypoglycemic episodes compared to patients treated with NovoLog® (insulin aspart injection); the imbalance was greater during the nocturnal period. Monitor blood glucose levels closely in pediatric patients.
- Like all insulins, Fiasp® requirements may be reduced in patients with renal impairment or hepatic impairment. These patients may require more frequent blood glucose monitoring and dose adjustments.

Please click here for Fiasp® Prescribing Information.

Indications and Usage for Tresiba® (insulin degludec) injection 100 U/mL, 200 U/mL

Tresiba® (insulin degludec) injection is indicated to improve glycemic control in patients 1 year of age and older with diabetes mellitus.

Limitations of Use

Tresiba® is not recommended for treating diabetic ketoacidosis.

Important Safety Information

Contraindications

- Tresiba® is contraindicated during episodes of hypoglycemia and in patients with hypersensitivity to insulin degludec or any of the excipients in Tresiba®

Warnings and Precautions

- **Never Share a Tresiba® FlexTouch® Pen, Needle, or Syringe Between Patients, even if the needle is changed.** Patients using Tresiba® vials should never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.
- **Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen:** Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, or injection site or method of administration) may affect glycemic control and predispose to hypoglycemia or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia. Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to

change the injection site to unaffected areas and closely monitor for hypoglycemia. Adjustments in concomitant anti-diabetic treatment may be needed.

- **Hypoglycemia:** Hypoglycemia is the most common adverse reaction of insulin, including Tresiba®. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place the patient and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). Hypoglycemia can happen suddenly and symptoms may differ in each patient and change over time in the same patient. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic neuropathy, using drugs that block the sympathetic nervous system (e.g., beta-blockers) or who experience recurrent hypoglycemia. The long-acting effect of Tresiba® may delay recovery from hypoglycemia compared to shorter-acting insulins.

  Risk Factors for Hypoglycemia: The risk of hypoglycemia generally increases with intensity of glycemic control. The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulins, the glucose lowering effect time course of Tresiba® may vary among different patients or at different times in the same patients and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature. Other factors which may increase the risk of hypoglycemia include changes in meal pattern, changes in level of physical activity, or changes to concomitant drugs. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia. Patients and caregivers must be educated to recognize and manage hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.
- **Hypoglycemia Due to Medication Errors:** Accidental mix-ups between insulin products have been reported. To avoid medication errors between Tresiba® and other insulins, always instruct patients to always check the insulin label before each injection. To avoid dosing errors and potential overdose, never use a syringe to remove Tresiba® from the Tresiba® FlexTouch® disposable insulin prefilled pen.
- **Hypersensitivity Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulins, including Tresiba®**.** If hypersensitivity reactions occur, discontinue Tresiba®; treat per standard of care and monitor until symptoms and signs resolve.

- **Hypokalemia:** All insulins, including Tresiba®, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated.
- **Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists:** Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including Tresiba®. Patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of the TZD must be considered.

Adverse Reactions

- Adverse reactions commonly associated with Tresiba® are hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema, and weight gain.

Drug Interactions

- There are certain drugs that may cause clinically significant drug interactions with Tresiba®.

  Drugs that may increase the risk of hypoglycemia: antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors

  Drugs that may decrease the blood glucose lowering effect: atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones

  Drugs that may increase or decrease the blood glucose lowering effect: alcohol, beta-blockers, clonidine, lithium salts, and pentamidine

  Drugs that may blunt the signs and symptoms of hypoglycemia: beta-blockers, clonidine, guanethidine, and reserpine

Please click here for Tresiba® Prescribing Information.