HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use TIRZEPEN safely and effectively. See full prescribing information for TIRZEPEN. TIRZEPEN® (tirzepatide) Injection, for subcutaneous use Initial U.S. Approval: 2022

WARNING: RISK OF THYROID C-CELL TUMORS See full prescribing information for complete boxed warning.
Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether TIRZEPEN causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).
TIRZEPEN is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1)

RECENT MAJOR CHANGES

Contraindications (4) 04/2023 Warnings and Precautions Hypersensitivity Reactions (5.4) 04/2023

---------- INDICATIONS AND USAGE ----------

TIRZEPEN® is a glucose-dependent insulinotropic polypeptide (GIP) receptor and 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: Has not been studied in patients with a history of pancreatitis (1, 5.2) Is not indicated for use in patients with type 1 diabetes mellitus (1)

----------DOSAGE AND ADMINISTRATION----------

The recommended starting dosage is 2.5 mg injected subcutaneously once weekly (2.1) After 4 weeks, increase to 5 mg injected subcutaneously once weekly (2.1) If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose. The maximum dosage is 15 mg subcutaneously once weekly (2.1). Administer once weekly at any time of day, with or without meals. (2.2) Inject subcutaneously in the abdomen, thigh, or upper arm. (2.2) Rotate injection sites with each dose.

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen or single-dose vial (3)

---------- CONTRAINDICATIONS ----------

 Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1) Known serious hypersensitivity to tirzepatide or any of the excipients in TIRZEPEN (4, 5.4)

----------WARNINGS AND PRECAUTIONS----------

 Pancreatitis: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. (5.2) Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: 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. (5.3) Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported.

----------ADVERSE REACTIONS----------

The most common adverse reactions, reported in ≥5% of patients treated with TIRZEPEN are: nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain. (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

TIRZEPEN delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

 Pregnancy: Based on animal study, may cause fetal harm. (8.1) Females of Reproductive Potential: Advise females using oral contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation. (7.2, 8.3, 12.3) See 17 for PATIENT COUNSELING INFORMATION and

FDAapproved Medication Guide. Revised: 07/2023

FULL PRESCRIBING INFORMATION: CONTENTS

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

 In both male and female rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether TIRZEPEN causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatideinduced rodent thyroid C-cell tumors has not been determined [see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)].

 TIRZEPEN 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 TIRZEPEN 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 TIRZEPEN [see Contraindications (4) and Warnings and Precautions (5.1)].

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

Limitations of Use

 TIRZEPEN has not been studied in patients with a history of pancreatitis [see Warnings and Precautions (5.2)]. TIRZEPEN is not indicated for use in patients with type 1 diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

 The recommended starting dosage of TIRZEPEN is 2.5 mg injected subcutaneously once weekly. The 2.5 mg dosage is for treatment initiation and is not intended for glycemic control.

 After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly.

 If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.

 The maximum dosage of TIRZEPEN is 15 mg injected subcutaneously once weekly.

 If a dose is missed, instruct patients to administer TIRZEPEN as soon as possible within 4 days (96 hours) after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule. 3

 The day of weekly administration can be changed, if necessary, as long as the time between the two doses is at least 3 days (72 hours).

2.2 Important Administration Instructions

 Prior to initiation, train patients and caregivers on proper injection technique [see Instructions for Use].

 Instruct patients using the single-dose vial to use a syringe appropriate for dose administration (e.g., a 1 mL syringe capable of measuring a 0.5 mL dose).

 Administer TIRZEPEN once weekly, any time of day, with or without meals.

 Inject TIRZEPEN subcutaneously in the abdomen, thigh, or upper arm.

 Rotate injection sites with each dose.

 Inspect TIRZEPEN visually before use. It should appear clear and colorless to slightly yellow. Do not use TIRZEPEN if particulate matter or discoloration is seen.

 When using TIRZEPEN with insulin, administer as separate injections and never mix. It is acceptable to inject TIRZEPEN and insulin in the same body region, but the injections should not be adjacent to each other.

3 DOSAGE FORMS AND STRENGTHS

Injection: Clear, colorless to slightly yellow solution in pre-filled single-dose pens or single-dose vials, each available in the following strengths:

 2.5 mg/0.5 mL
 5 mg/0.5 mL
 7.5 mg/0.5 mL
 10 mg/0.5 mL
 12.5 mg/0.5 mL
 15 mg/0.5 mL

4 CONTRAINDICATIONS TIRZEPEN 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 serious hypersensitivity to tirzepatide or any of the excipients in TIRZEPEN. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with TIRZEPEN [see Warnings and Precautions (5.4)].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors In both sexes of rats, tirzepatide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) in a 2-year study at clinically relevant plasma exposures [see Nonclinical Toxicology (13.1)]. It is unknown whether TIRZEPEN causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined. TIRZEPEN 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 TIRZEPEN 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 TIRZEPEN. 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 values 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 Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists. In clinical studies, 14 events of acute pancreatitis were confirmed by adjudication in 13 TIRZEPEN-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 comparator-treated patients (0.11 patients per 100 years of exposure). TIRZEPEN has not been studied in patients with a prior history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on TIRZEPEN. After initiation of TIRZEPEN, 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 TIRZEPEN and initiate appropriate management.

5.3 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin Patients receiving TIRZEPEN 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), Drug Interactions (7.1)]. 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.

5.4 Hypersensitivity Reactions Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with TIRZEPEN. If hypersensitivity reactions occur, discontinue use of TIRZEPEN; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous serious hypersensitivity reaction to tirzepatide or any of the excipients in TIRZEPEN [see Contraindications (4), Adverse Reactions (6.2)]. Anaphylaxis and angioedema have been reported with GLP-1 receptor agonists. Use caution in patients with a history of angioedema or anaphylaxis with a GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with MOUNJARO.

5.5 Acute Kidney Injury TIRZEPEN has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhea [see Adverse Reactions (6.1)]. These events may lead to dehydration, which if severe could cause acute kidney injury. In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis. 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 TIRZEPEN in patients with renal impairment reporting severe gastrointestinal adverse reactions.

5.6 Severe Gastrointestinal Disease Use of TIRZEPEN has been associated with gastrointestinal adverse reactions, sometimes severe [see Adverse Reactions 6.1].

TIRZEPEN has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

5.7 Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. TIRZEPEN has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

5.8 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 TIRZEPEN placebo-controlled clinical trials, acute gallbladder disease (cholelithiasis, biliary colic, and cholecystectomy) was reported by 0.6% of TIRZEPEN-treated patients and 0% of placebo-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

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)] Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin [see Warnings and Precautions (5.3)]

 Hypersensitivity Reactions [see Warnings and Precautions (5.4)]

 Acute Kidney Injury [see Warnings and Precautions (5.5)] Severe Gastrointestinal Disease [see Warnings and Precautions (5.6)]

 Diabetic Retinopathy Complications [see Warnings and Precautions (5.7)]

 Acute Gallbladder Disease [see Warnings and Precautions (5.8)] 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 Two Placebo-Controlled Clinical Trials The data in Table 1 are derived from 2 placebo-controlled trials [1 monotherapy trial (SURPASS-1) and 1 trial in combination with basal insulin with or without metformin (SURPASS-5)] in adult patients with type 2 diabetes mellitus [see Clinical Studies (14.2, 14.4)]. These data reflect exposure of 718 patients to TIRZEPEN and a mean duration of exposure to TIRZEPEN of 36.6 weeks. The mean age of patients was 58 years, 4% were 75 years or older and 54% were male. The population was 57% White, 27% Asian, 13% American Indian or Alaska Native, and 3% Black or African American; 25% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes mellitus for an average of 9.1 years with a mean HbA1c of 8.1%. As assessed by baseline fundoscopic examination, 13% of the population had retinopathy. At baseline, eGFR was ≥90 mL/min/1.73 m2 in 53%, 60 to 90 mL/min/1.73 m2 in 39%, 45 to 60 mL/min/1.73 m2 in 7%, and 30 to 45 mL/min/1.73 m2 in 1% of patients.

Pool of Seven Controlled Clinical Trials Adverse reactions were also evaluated in a larger pool of adult patients with type 2 diabetes mellitus participating in seven controlled clinical trials which included two placebo-controlled trials (SURPASS-1 and -5), three trials of TIRZEPEN in combination with metformin, sulfonylureas, and/or SGLT2 Inhibitors (SURPASS-2, -3, -4) [see Clinical Studies (14.3)] and two additional trials conducted in Japan. In this pool, a total of 5119 adult patients with type 2 diabetes mellitus were treated with TIRZEPEN for a mean duration of 48.1 weeks. The mean age of patients was 58 years, 4% were 75 years or older and 58% were male. The population was 65% White, 24% Asian, 7% American Indian or Alaska Native, and 3% Black or African American; 38% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes mellitus for an average of 9.1 years with a mean HbA1c of 8.3%. As assessed by baseline fundoscopic examination, 15% of the population had retinopathy. At baseline, eGFR was ≥90 mL/min/1.73 m2 in 52%, 60 to 90 mL/min/1.73 m2 in 40%, 45 to 60 mL/min/1.73 m2 in 6%, and 30 to 45 mL/min/1.73 m2 in 1% of patients. Common Adverse Reactions Table 1 shows common adverse reactions, not including hypoglycemia, associated with the use of TIRZEPEN in the pool of placebo-controlled trials. These adverse reactions occurred more commonly on TIRZEPEN than on placebo and occurred in at least 5% of patients treated with TIRZEPEN.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of TIRZEPEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Hypersensitivity: anaphylaxis, angioedema Gastrointestinal: ileus

7 DRUG INTERACTIONS

7.1 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin When initiating TIRZEPEN, consider reducing the dose of concomitantly administered insulin secretagogues (e.g., sulfonylureas) or insulin to reduce the risk of hypoglycemia [see Warnings and Precautions (5.3)].

7.2 Oral Medications TIRZEPEN delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with TIRZEPEN. Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with TIRZEPEN. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with TIRZEPEN. Hormonal contraceptives that are not administered orally should not be affected [see Use in Specific Populations (8.3) and Clinical Pharmacology (12.2, 12.3)]. 8

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary Available data with TIRZEPEN use in pregnant women are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations).

Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. TIRZEPEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In pregnant rats administered tirzepatide during organogenesis, fetal growth reductions and fetal abnormalities occurred at clinical exposure in maternal rats based on AUC. In rabbits administered tirzepatide during organogenesis, fetal growth reductions were observed at clinically relevant exposures based on AUC. These adverse embryo/fetal effects in animals coincided with pharmacological effects on maternal weight and food consumption (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 >10%. The estimated background risk of miscarriage for the indicated population is unknown. 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/or Embryo/Fetal Risk Poorly controlled diabetes in 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 pregnant rats given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide (0.03-, 0.07-, and 0.5-fold the MRHD of 15 mg once weekly based on AUC) during organogenesis, increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and decreased fetal weights coincided with pharmacologically-mediated reductions in maternal body weights and food consumption at 0.5 mg/kg. In pregnant rabbits given once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg tirzepatide (0.01-, 0.06-, and 0.2-fold the MRHD) during organogenesis, pharmacologically-mediated effects on the gastrointestinal system resulting in maternal mortality or abortion in a few rabbits occurred at all dose levels. Reduced fetal weights associated with decreased maternal food consumption and body weights were observed at 0.1 mg/kg. In a pre- and post-natal study in rats administered subcutaneous doses of 0.02, 0.10, or 0.25 mg/kg tirzepatide twice weekly from implantation through lactation, F1 pups from F0 maternal rats given 0.25 mg/kg tirzepatide had statistically significant lower mean body weight when compared to controls from post-natal day 7 through post-natal day 126 for males and post-natal day 56 for females.

8.2 Lactation Risk Summary There are no data on the presence of tirzepatide in animal or human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TIRZEPEN and any potential adverse effects on the breastfed infant from TIRZEPEN or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential Contraception Use of TIRZEPEN may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying. This delay is largest after the first dose and diminishes over time. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with TIRZEPEN [see Drug Interactions (7.2) and Clinical Pharmacology (12.2, 12.3)]. 8.4 Pediatric Use Safety and effectiveness of TIRZEPEN have not been established in pediatric patients (younger than 18 years of age). 9

8.5 Geriatric Use In the pool of seven clinical trials, 1539 (30.1%) TIRZEPEN-treated patients were 65 years of age or older, and 212 (4.1%) TIRZEPEN-treated patients were 75 years of age or older at baseline. No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment No dosage adjustment of TIRZEPEN is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no change in tirzepatide pharmacokinetics (PK) was observed [see Clinical Pharmacology (12.3)]. Monitor renal function when initiating or escalating doses of TIRZEPEN in patients with renal impairment reporting severe adverse gastrointestinal reactions [see Warnings and Precautions (5.5)]. 8.7 Hepatic Impairment No dosage adjustment of TIRZEPEN is recommended for patients with hepatic impairment. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no change in tirzepatide PK was observed [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE

In the event of an overdosage, contact Poison Control for latest recommendations. Appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A period of observation and treatment for these symptoms may be necessary, taking into account the half-life of tirzepatide of approximately 5 days.

11 DESCRIPTION MOUNJARO (tirzepatide) injection, for subcutaneous use, contains tirzepatide, a once weekly GIP receptor and GLP-1 receptor agonist. It is a 39-amino-acid modified peptide based on the GIP sequence. Tirzepatide contains 2 non-coded amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 that is attached to 1,20-eicosanedioic acid via a linker. The molecular weight is 4813.53 Da and the empirical formula is C225H348N48O68.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It is a 39-amino-acid modified peptide with a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1. Tirzepatide enhances first- and second-phase insulin secretion, and reduces glucagon levels, both in a glucosedependent manner. 10

12.2 Pharmacodynamics Tirzepatide lowers fasting and postprandial glucose concentration, decreases food intake, and reduces body weight in patients with type 2 diabetes mellitus. First and Second-Phase Insulin Secretion Tirzepatide enhances the first- and second-phase insulin secretion.

Insulin Sensitivity Tirzepatide increases insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study after 28 weeks of treatment. Glucagon Secretion Tirzepatide reduces fasting and postprandial glucagon concentrations. Tirzepatide 15 mg reduced fasting glucagon concentration by 28% and glucagon AUC after a mixed meal by 43%, compared with no change for placebo after 28 weeks of treatment. Gastric Emptying Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time. Tirzepatide slows post-meal glucose absorption, reducing postprandial glucose.

12.3 Pharmacokinetics The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with type 2 diabetes mellitus. Steadystate plasma tirzepatide concentrations were achieved following 4 weeks of once weekly administration. Tirzepatide exposure increases in a dose-proportional manner. Absorption Following subcutaneous administration, the time to maximum plasma concentration of tirzepatide ranges from 8 to 72 hours. The mean absolute bioavailability of tirzepatide following subcutaneous administration is 80%. Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm. 11 Distribution The mean apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with type 2 diabetes mellitus is approximately

10.3 L. Tirzepatide is highly bound to plasma albumin (99%). Elimination The apparent population mean clearance of tirzepatide is 0.061 L/h with an elimination half-life of approximately 5 days, enabling once-weekly dosing. Metabolism Tirzepatide is metabolized by proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis. Excretion The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces. Specific Populations The intrinsic factors of age, gender, race, ethnicity, or body weight do not have a clinically relevant effect on the PK of tirzepatide. Patients with Renal Impairment Renal impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. This was also shown for patients with both type 2 diabetes mellitus and renal impairment based on data from clinical studies [see Use in Specific Populations (8.6)]. Patients with Hepatic Impairment Hepatic impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function [see Use in Specific Populations (8.7)]. Drug Interactions Studies Potential for Tirzepatide to Influence the Pharmacokinetics of Other Drugs In vitro studies have shown low potential for tirzepatide to inhibit or induce CYP enzymes, and to inhibit drug transporters. TIRZEPEN delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications [see Drug Interactions (7.2)]. The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses. Following a first dose of tirzepatide 5 mg, acetaminophen maximum concentration (Cmax) was reduced by 50%, and the median peak plasma concentration (tmax) occurred 1 hour later. After coadministration at week 4, there was no meaningful impact on acetaminophen Cmax and tmax. Overall acetaminophen exposure (AUC0-24hr) was not influenced. Following administration of a combined oral contraceptive (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single dose of tirzepatide 5 mg, mean Cmax of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%,66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in tmax of 2.5 to 4.5 hours was observed.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the trials described below with the incidence of anti-drug antibodies in other trials. During the 40- to 104-week treatment periods with ADA sampling conducted up to 44 to 108 weeks in seven clinical trials in adults with type 2 diabetes mellitus [see Clinical Studies (14)], 51% (2,570/5,025) of TIRZEPEN-treated patients developed anti-tirzepatide antibodies. In these trials, anti-tirzepatide antibody formation in 34% and 14% of TIRZEPENtreated patients showed cross-reactivity to native GIP or native GLP-1, respectively. Of the 2,570 TIRZEPEN-treated patients who developed anti-tirzepatide antibodies during the treatment periods in these seven trials, 2% and 2% developed neutralizing antibodies against tirzepatide activity on the GIP or GLP-1 receptors, respectively, and 0.9% and 0.4% developed neutralizing antibodies against native GIP or GLP-1, respectively. 12 There was no identified clinically significant effect of anti-tirzepatide antibodies on pharmacokinetics or effectiveness of TIRZEPEN. More TIRZEPEN-treated patients who developed anti-tirzepatide antibodies experienced hypersensitivity reactions or injection site reactions than those who did not develop these antibodies [see Adverse Reactions (6.1)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.1-, 0.4-, and 1-fold the MRHD of 15 mg once weekly based on AUC) administered by subcutaneous injection twice weekly. A statistically significant increase in thyroid C-cell adenomas was observed in males (≥0.5 mg/kg) and females (≥0.15 mg/kg), and a statistically significant increase in thyroid C-cell adenomas and carcinomas combined was observed in males and females at all doses examined. In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered by subcutaneous injection twice weekly was not tumorigenic. Tirzepatide was not genotoxic in a rat bone marrow micronucleus assay. In fertility and early embryonic development studies, male and female rats were administered twice weekly subcutaneous doses of 0.5, 1.5, or 3 mg/kg (0.3-, 1-, and 2-fold and 0.3-, 0.9-, and 2-fold, respectively, the MRHD of 15 mg once weekly based on AUC). No effects of tirzepatide were observed on sperm morphology, mating, fertility, and conception. In female rats, an increase in the number of females with prolonged diestrus and a decrease in the mean number of corpora lutea resulting in a decrease in the mean number of implantation sites and viable embryos was observed at all dose levels. These effects were considered secondary to the pharmacological effects of tirzepatide on food consumption and body weight.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies The effectiveness of TIRZEPEN as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus was established in five trials. In these trials, TIRZEPEN was studied as monotherapy (SURPASS-1); as an add-on to metformin, sulfonylureas, and/or sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) (SURPASS-2, -3, and -4); and in combination with basal insulin with or without metformin (SURPASS-5).

In these trials, TIRZEPEN (5 mg, 10 mg, and 15 mg given subcutaneously once weekly) was compared with placebo, semaglutide 1 mg, insulin degludec, and/or insulin glargine. In adult patients with type 2 diabetes mellitus, treatment with TIRZEPEN produced a statistically significant reduction from baseline in HbA1c compared to placebo. The effectiveness of TIRZEPEN was not impacted by age, gender, race, ethnicity, region, or by baseline BMI, HbA1c, diabetes duration, or renal function. 14.2 Monotherapy Use of TIRZEPEN in Adult Patients with Type 2 Diabetes Mellitus SURPASS-1 (NCT03954834) was a 40-week double-blind trial that randomized 478 adult patients with type 2 diabetes mellitus with inadequate glycemic control with diet and exercise to TIRZEPEN 5 mg, TIRZEPEN 10 mg, TIRZEPEN 15 mg, or placebo once weekly. Patients had a mean age of 54 years, and 52% were men. The mean duration of type 2 diabetes mellitus was 4.7 years, and the mean BMI was 32 kg/m2 . Overall, 36% were White, 35% were Asian, 25% were American Indians/Alaska Natives, and 5% were Black or African American; 43% identified as Hispanic or Latino ethnicity. Monotherapy with TIRZEPEN 5 mg, 10 mg and 15 mg once weekly for 40 weeks resulted in a statistically significant reduction in HbA1c compared with placebo.

14.3 TIRZEPEN Use in Combination with Metformin, Sulfonylureas, and/or SGLT2 Inhibitors in Adult Patients with Type 2 Diabetes Mellitus Add-on to metformin SURPASS-2 (NCT03987919) was a 40-week open-label trial (double-blind with respect to TIRZEPEN dose assignment) that randomized 1879 adult patients with type 2 diabetes mellitus with inadequate glycemic control on stable doses of metformin alone to the addition of TIRZEPEN 5 mg, TIRZEPEN 10 mg, or TIRZEPEN 15 mg once weekly or subcutaneous semaglutide 1 mg once weekly. Patients had a mean age of 57 years and 47% were men. The mean duration of type 2 diabetes mellitus was 8.6 years, and the mean BMI was 34 kg/m2 . Overall, 83% were White, 4% were Black or African American, and 1% were Asian; 70% identified as Hispanic or Latino ethnicity. Treatment with TIRZEPEN 10 mg and 15 mg once weekly for 40 weeks resulted in a statistically significant reduction in HbA1c compared with semaglutide 1 mg once weekly.

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Use in Combination with Basal Insulin with or without Metformin in Adult Patients with Type 2 Diabetes Mellitus SURPASS-5 (NCT04039503) was a 40-week double-blind trial that randomized 475 patients with type 2 diabetes mellitus with inadequate glycemic control on insulin glargine 100 units/mL, with or without metformin, to TIRZEPEN 5 mg, TIRZEPEN 10 mg, TIRZEPEN 15 mg once weekly, or placebo. The dose of background insulin glargine was adjusted using a treat-to-target algorithm based on self-measured fasting blood glucose values, targeting <100 mg/dL. 17 Patients had a mean age of 61 years, and 56% were men. The mean duration of type 2 diabetes mellitus was 13.3 years, and the mean baseline BMI was 33 kg/m2 . Overall, 80% were White, 1% were Black or African American, and 18% were Asian; 5% identified as Hispanic or Latino ethnicity. The mean dose of insulin glargine at baseline was 34, 32, 35, and 33 units/day for patients receiving TIRZEPEN 5 mg, 10 mg, 15 mg, and placebo, respectively. At randomization, the initial insulin glargine dose in patients with HbA1c ≤8.0% was reduced by 20%. At week 40, mean dose of insulin glargine was 38, 36, 29, and 59 units/day for patients receiving TIRZEPEN 5 mg, 10 mg, 15 mg, and placebo, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

 Store TIRZEPEN in a refrigerator at 2°C to 8°C (36°F to 46°F).

 If needed, each single-dose pen or single-dose vial can be stored unrefrigerated at temperatures not to exceed 30ºC (86ºF) for up to 21 days.

 Do not freeze TIRZEPEN. Do not use TIRZEPEN if frozen.

 Store TIRZEPEN in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use). Risk of Thyroid C-Cell Tumors Inform patients that TIRZEPEN causes thyroid C-cell tumors in rats 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, persistent hoarseness, dysphagia, or dyspnea) to their healthcare provider [see Boxed Warning and Warnings and Precautions (5.1)]. Pancreatitis Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue TIRZEPEN promptly and contact their healthcare provider 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)]. Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin Inform patients that the risk of hypoglycemia is increased when TIRZEPEN 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 (5.3)]. Hypersensitivity Reactions Inform patients that serious hypersensitivity reactions have been reported with use of TIRZEPEN. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking TIRZEPEN and seek medical advice promptly if such symptoms occur [see Warnings and Precautions (5.4)]. Acute Kidney Injury Advise patients treated with TIRZEPEN 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]. Severe Gastrointestinal Adverse Reactions Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms [see Warnings and Precautions (5.6)]. Diabetic Retinopathy Complications Inform patients to contact their healthcare provider if changes in vision are experienced during treatment with TIRZEPEN [see Warnings and Precautions (5.7]. Acute Gallbladder Disease Inform patients of the risk of acute gallbladder disease. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected [see Warnings and Precautions (5.8)]. 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)]. 19 Contraception Use of TIRZEPEN may reduce the efficacy of oral hormonal contraceptives. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with TIRZEPEN [see Drug Interactions (7.2), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)].

Administration Instruct patients how to prepare and administer the correct dose of TIRZEPEN and assess their ability to inject subcutaneously to ensure the proper administration of TIRZEPEN. Instruct patients using the single-dose vial to use a syringe appropriate for dose administration (e.g., a 1 mL syringe capable of measuring a 0.5 mL dose) [see Dosage and Administration (2.2)]. Missed Doses Inform patients if a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, inform patients to resume their regular once weekly dosing schedule [see Dosage and Administration (2.1)].

Tirzepen®