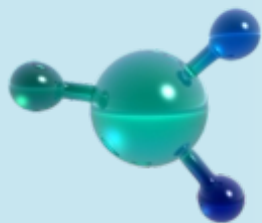


TIRZEPATIDE

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TIRZEPATIDE

Tirzepatide: What is it indicated for and what does it do?

It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Tirzepatide is used for weight loss, to help lose weight and maintain weight. Tirzepatide works for weight loss by decreasing appetite and slowing the movement of food from the stomach to the small intestine, which can make you feel full more quickly and for a longer period of time.

Tirzepatide is an injection given once a week under the skin using a pen (auto-injector).

The active substance Tirzepatide is used for type 2 diabetes to help improve blood sugar levels.

In type 2 diabetes, Tirzepatide lowers blood sugar levels by helping to release insulin when blood sugar levels are high, decreasing the amount of sugar produced by the liver, and slowing the movement of food through the intestines. Tirzepatide should be used in conjunction with diet and exercise.

Tirzepatide has been approved by the FDA (the health regulatory agency in the United States) to treat adults with type 2 diabetes and should be used alongside diet and exercise. It can be used as a single therapy (on its own) or with other diabetes medications, including sulfonylureas, SGLT2 inhibitors, or metformin.

It is unknown whether Tirzepatide can be used in individuals who have had pancreatitis. Tirzepatide should not be used in people with type 1 diabetes.

Tirzepatide is made by Eli Lilly and Company. In Brazil, it is available as single-dose pens in the same dosages of 5 mg, 10 mg, 15 mg, and 20 mg per 0.5 mL.

Tirzepatide has been approved by Anvisa, the National Health Surveillance Agency (Anvisa) granted the sanitary registration MS No. 1.1260.0202 for the drug Tirzepatide in the Official Gazette No. 183 on 09/25/2023, through Resolution-RE No. 3.591 of 09/21/2023.



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The documentation presented meets the current legislation, Law No. 6.360/1976, Decree No. 8.077/2013, Law No. 9.787/1999, Resolution RDC No. 200/2017, among other related regulations.

The available opinions do not undergo updates after the granting of the registration. However, information regarding presentation, packaging, manufacturing location, expiration date, and storage precautions, as well as package insert texts, can be consulted at the link:

<https://consultas.anvisa.gov.br/#/medicamentos/>

How does Tirzepatide work?

Normally, when we eat, natural hormones called GIP and GLP-1 are released by the intestine. These hormones increase insulin release, suppress appetite, slow gastric emptying, and increase feelings of fullness. Tirzepatide works like our natural hormones GIP and GLP-1 by activating the GIP and GLP-1 receptors.

Tirzepatide is a GIP and GLP-1 receptor agonist. Tirzepatide works (mechanism of action) by activating the hormonal GIP (glucose-dependent insulinitropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptors.

How much weight is lost during treatment?

Patients on Tirzepatide 5 mg per week lost an average of 16.1 kg (35.5 lb) after 72 weeks. For the weekly dose of 10 mg of Tirzepatide, the average weight loss was 22.2 kg (48.9 lb), and for the weekly dose of 15 mg of Tirzepatide, the average weight loss was 23.6 kg (52.0 lb) over 72 weeks. Patients who used a placebo lost 2.4 kg (5.3 lb) over 72 weeks. These results are from the clinical trial SURMOUNT-1, NCT04184622. Individual results may vary.

What are the contraindications for Tirzepatide?

Hypersensitivity to the components of the formula.

How to use Tirzepatide?

You should carefully follow the instructions on your prescription label and ask your pharmacist or doctor to explain any part you do not understand. It is important to use this medication exactly as directed. Do not take more or less or take it more often than prescribed by your doctor.

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Tirzepatide is an injection given once a week under the skin (subcutaneously) using a pre-filled single-dose pen.

Usually given:

- Once a week.
- Can be administered with or without meals at any time of the day.
- Can be injected in the thigh, abdomen, or upper arm.
- You should rotate injection sites with each dose.

Your doctor will likely start you on a low dose, which can be gradually increased, but not more than once every 4 weeks.

You can change the day of the week you use Tirzepatide as long as there are at least three days between doses.

You can administer insulin in the same area as Tirzepatide, but they should not be given next to each other. Insulin and Tirzepatide should be administered as separate injections and should not be mixed in the same injection.

Tirzepatide controls type 2 diabetes but does not cure it. It may take four weeks or more before you see the full benefit of this medication. Continue taking this medication even if you feel well. Do not stop taking this medication without talking to your doctor.

Medications containing the active substance Tirzepatide should be administered subcutaneously in the abdomen, thigh, or arm. The injection site should be alternated.

The initial dose of Tirzepatide is 2.5 mg once a week. After 4 weeks, the dose should be increased to 5 mg once a week. If necessary, dose increases can be made in increments of 2.5 mg after a minimum of 4 weeks at the current dose. The maximum dose of Tirzepatide is 15 mg once a week. Dose adjustments based on age, gender, race, ethnicity, body weight, or hepatic or renal insufficiency (including end-stage renal disease) are not necessary.

The safety and efficacy of Tirzepatide have not been established in patients under 18 years of age.

Information on Tirzepatide dosing

Usual Dose of Tirzepatide for Weight Loss (Adult)

- **Initial dose:** 2.5 mg subcutaneously once a week.
- **After 4 weeks:** The dose should be increased to 5 mg subcutaneously once a week.

Information on Tirzepatide dosing

Usual Dose of Tirzepatide for Weight Loss (Adult)

- **Additional dose increases:** After at least 4 weeks at the current dose, the dosage may be increased in increments of 2.5 mg.
- **Recommended maintenance dose:** 5 mg, 10 mg, or 15 mg injected subcutaneously once a week.
- **Maximum dose:** 15 mg subcutaneously once a week.

Usual Dose of Tirzepatide for Type 2 Diabetes (Adult)

- **Initial dose:** 2.5 mg subcutaneously once a week.
- **After 4 weeks:** The dose should be increased to 5 mg subcutaneously once a week.
- **If additional glycemic control is needed:** The dosage should be increased in increments of 2.5 mg after at least 4 weeks at the current dose.
- **Maximum dose:** 15 mg subcutaneously once a week.

The 2.5 mg dose is for treatment initiation and is not intended for glycemic control. The day of weekly administration may be changed if necessary, provided that the time between the two doses is at least 3 days (72 hours).

What should I do if I miss a dose?

If you miss a dose of Tirzepatide, take the missed dose as soon as you remember, if within 4 days of the missed dose. However, if more than 4 days have passed since your last dose, skip the missed dose and continue your regular dosing schedule. Do not inject two doses within 3 days of each other.

For Healthcare Professionals

Applies to Tirzepatide: subcutaneous solution.

What are the adverse reactions and side effects of Tirzepatide?

Common side effects of Tirzepatide

The most common side effects of Tirzepatide include abdominal pain, belching, constipation, diarrhea, dyspepsia, fatigue, gastroesophageal reflux disease, hair loss, hypersensitivity reactions, injection site reactions, nausea, and vomiting, affecting 5% or more of patients.

Serious side effects of Tirzepatide

Stop using this medication and seek emergency medical help if you have:

- Signs of an allergic reaction: hives; difficulty breathing; feeling faint; swelling of the face, lips, tongue, or throat; or
-
- Pancreatitis with symptoms of severe pain in the upper stomach radiating to the back, nausea, and vomiting.

Call your doctor immediately if you have:

- Severe stomach problems;
- Eye side effects or changes in vision, including blurred vision;
- Signs of thyroid tumor symptoms may include swelling or a lump in the neck, difficulty swallowing, a hoarse voice, or feeling short of breath;
- Gallbladder problems with symptoms including chalky stools, stomach pain after eating, nausea, heartburn, bloating, and severe upper stomach pain that may radiate to the back;
- Symptoms of low blood sugar may include headache, hunger, weakness, sweating, confusion, irritability, dizziness, rapid heartbeat, or feeling nervous; or
- Kidney problems with little or no urination, swelling in the feet or ankles, feeling tired, or shortness of breath.

This is not a complete list of side effects, and others may occur. Call your doctor for medical advice about side effects.

Tirzepatide may cause other side effects. Call your doctor if you have any unusual problems while taking this medication. If you experience a serious side effect, you or your doctor may report it to VigiMed at Anvisa.

Other Serious side effects of Tirzepatide

Along with its necessary effects, Tirzepatide may cause some unwanted effects. Although not all of these side effects may occur, if they do occur, they may require medical attention.

Check with your doctor immediately if any of the following side effects occur while taking Tirzepatide.

More common

- Stomach pain.

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Less common

- Difficulty breathing or swallowing;

- Rapid heartbeat;
- Gas pain in the stomach;
- Heartburn;
- Recurring fever;
- Skin itching, rash, or redness;
- Fullness in the stomach;
- Swelling of the face, throat, or tongue;
- Vomiting;
- Yellowing of the eyes or skin.

Incidence unknown

- Anxiety;
- Swelling;
- Blurred vision;
- Change in vision;
- Behavioral changes;
- Tightness in the chest;
- Chills;
- Cold sweats;
- Coma;
- Confusion;
- Constipation;
- Cool, pale skin;
- Cough;
- Dark urine;
- Depression;
- Dizziness;
- Rapid heartbeat;
- Fever;
- Increased appetite;
- Indigestion;
- Large swelling resembling hives on the face, eyelids, lips, tongue, throat, hands, legs, feet, or genital organs;
- Loss of appetite;
- Nausea;
- Nervousness;
- Nightmares;
- Stomach, side, or abdominal pain, possibly radiating to the back;
- Swelling or puffiness of the eyelids or around the eyes, face, lips, or tongue;
- Seizures;
- Tremors;
- Slurred speech;
- Thoughts of self-harm;
- Unusual tiredness or weakness.

Other Side Effects of Tirzepatide II

Some side effects of Tirzepatide may occur that generally **do not require medical attention**. These side effects may disappear during treatment as your body adjusts to the medication. Additionally, your healthcare professional may be able to tell you about ways to prevent or reduce some of these side effects.

Check with your healthcare professional if any of the following side effects **persist or are bothersome**, or if you have any questions about them:

More common

- Acid or sour stomach;
- Belching;
- Constipation;
- Diarrhea;
- Discomfort or unease in the stomach.

Less common

- Bleeding;
- Blisters;
- Burning;
- Coldness;
- Skin discoloration;
- Sensation of pressure;
- Hives;
- Infection;
- Inflammation;
- Itching;
- Bumps;
- Numbness;
- Pain;
- Rash;
- Redness;
- Scarring;
- Stinging;
- Swelling;
- Sensitivity;
- Tingling;
- Ulceration or warmth at the injection site.

For Healthcare Professionals

The most common adverse reactions reported in 5% or more of patients treated with this medication included nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain.

Cardiovascular

- **Very common (10% or more):** Sinus tachycardia (up to 23%);
- **Unreported frequency:** Increased heart rate.

In pooled placebo-controlled trials, treatment with this medication resulted in an average increase in heart rate of 2 to 4 beats per minute compared to an average increase of 1 beat per minute in patients treated with placebo. Episodes of sinus tachycardia (associated with a concomitant increase in heart rate of at least 15 beats per minute from baseline) were reported in up to 23% of patients. The clinical relevance of the increase in heart rate was uncertain.

Gastrointestinal

- **Very common (10% or more):** Nausea (up to 18%), diarrhea (up to 17%);
- **Common (1% to 10%):** Vomiting, constipation, dyspepsia, abdominal pain, belching, flatulence, gastroesophageal reflux disease, abdominal distension;
- **Uncommon (0.1% to 1%):** Cholelithiasis, acute pancreatitis, increased serum levels of pancreatic amylase, increased serum levels of lipase, acute gallbladder disease (including cholelithiasis, biliary colic, and cholecystectomy).
- **Post-marketing reports:** Ileus.

In pooled placebo-controlled trials, treatment with this medication resulted in average increases from baseline in serum levels of pancreatic amylase of up to 38% and serum levels of lipase of up to 42%; patients treated with placebo had an average increase from baseline in pancreatic amylase of 4%, and no change was observed in lipase. The clinical significance of elevations in lipase or amylase with this drug was unknown without other signs/symptoms of pancreatitis.

Hepatic

- **Uncommon (0.1% to 1%):** Acute gallbladder disease (cholelithiasis, biliary colic, cholecystectomy).

Hypersensitivity

- **Common (1% to 10%):** Hypersensitivity reactions (e.g., hives, eczema);
- **Post-marketing reports:** Anaphylaxis, angioedema.

Immunological

- **Very common (10% or more):** Drug antibodies (up to 51%);
- **Common (1% to 10%):** Neutralizing antibodies.

Local

- **Common (1% to 10%):** Injection site reactions.

Metabolic

- **Very common (10% or more): Hypoglycemia** (up to 19%), decreased appetite (up to 11%);
- **Common (1% to 10%):** Hyperglycemia.

Hypoglycemia (glucose level below 54 mg/dL) occurred more frequently when this medication was used in combination with a sulfonylurea (up to 13% of patients in a clinical trial); severe hypoglycemia occurred in up to 6% of patients. Hyperglycemia occurred more frequently in the placebo group than in patients treated with this medication.

Others

- **Common (1% to 10%):** Fatigue, including asthenia, malaise, lethargy;
- **Uncommon (0.1% to 1%):** Increased calcitonin in the blood.

Renal

- **Post-marketing reports** (in other GLP-1 receptor agonists): Acute kidney injury, worsening of chronic kidney disease.

Respiratory

- **Very common (10% or more):** Nasopharyngitis (10.5%).

Overdose: What happens if you take a dose of Tirzepatide greater than the recommended?

If you think you or someone else may have overdosed, call a doctor or poison control at 0800-722-6001.

If someone faints or has difficulty breathing after taking the medication, call 190 immediately.

Risks of Tirzepatide?

Toxicology

Preclinical data do not reveal special risks to humans based on conventional pharmacological safety studies, repeated dose toxicity, or genotoxicity conducted with Tirzepatide.

Carcinogenicity

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 [0.12, 0.36, and 1.02 times the maximum recommended human dose (MRHD) based on area under the curve (AUC)], administered by subcutaneous injection twice a week. Tirzepatide caused an increase in thyroid C-cell tumors (adenomas and carcinomas) at

Riscos do Tirzepatida?

Dose Usual de Tirzepatida para Perda de Peso (Adulto)

all doses compared to controls. The relevance of these findings to humans is unknown. In a 6-month carcinogenicity study in transgenic rasH2 mice, Tirzepatide at doses of 1, 3, and 10 mg/Kg, administered by subcutaneous injection twice a week, did not produce increased incidences of hyperplasia or thyroid neoplasia of C-cells at any dose.

Reproductive and Developmental Toxicity

Studies with Tirzepatide in animals did not indicate direct harmful effects related to fertility. In reproductive toxicity studies, Tirzepatide, at doses toxic to the mother, caused malformations, developmental variations, and reduced fetal growth.

Warnings

Subcutaneous Route (Solution)

Risk of thyroid C-cell tumors: In male and female rats, Tirzepatide causes dose-dependent and treatment duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Tirzepatide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of Tirzepatide-induced thyroid C-cell tumors in rodents has not been determined. Tirzepatide is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia type 2 (MEN 2). Advise patients about the potential risk of MTC with the use of Tirzepatide and inform them of the symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or the use of thyroid ultrasound has uncertain value for the early detection of MTC in patients treated with Tirzepatide.

Tirzepatide may cause thyroid C-cell tumors. It is important to tell your doctor if you or your family have a history of thyroid cancer or a condition called Multiple Endocrine Neoplasia (MEN). This is a syndrome that causes tumors to develop in the endocrine glands. If you experience any of these symptoms: a lump or swelling in the neck, difficulty swallowing, hoarseness, or shortness of breath, you should call your doctor immediately.

Keep all appointments with your doctor, healthcare professionals, and the laboratory. Your doctor may request certain tests to check your body's response to this medication.

Pregnancy Warnings with Tirzepatide

This medication should be used during pregnancy only if the benefit outweighs the risk to the fetus.

According to some authorities: The use of this medication is not recommended during pregnancy or in women with the potential to become pregnant who do not use contraception.

- **AU TGA pregnancy category:** D;
- **FDA pregnancy category:** Not assigned.
- **Risk summary:** Insufficient data available on the use of this medication in pregnant women to inform a drug-related risk; based on animal data, this medication may cause fetal harm.

Comments

- There are risks to the mother and fetus associated with uncontrolled diabetes in pregnancy.
- The use of this medication may reduce the effectiveness of oral hormonal contraceptives due to delayed gastric emptying; this delay is greater after the first dose and decreases over time. Patients using oral hormonal contraceptives should be advised to switch to a non-oral contraceptive method or add a barrier contraceptive method for 4 weeks after initiation and for 4 weeks after each dose increase with this medication.

Animal studies have revealed evidence of teratogenicity, fetotoxicity, and abortion when this medication was administered to pregnant animals during organogenesis at clinically relevant exposures based on AUC. These adverse embryofetal effects in animals coincided with pharmacological effects on maternal weight and food consumption. Studies in animals with this medication did not indicate direct harmful effects related to fertility. There are no controlled data in human pregnancy.

Uncontrolled diabetes in pregnancy increases the maternal risk of diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm birth, and delivery complications; uncontrolled diabetes increases the fetal risk of major congenital defects, stillbirth, and morbidity related to macrosomia.

AU TGA pregnancy category D: Drugs that have caused, are suspected of causing, or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Follow-up texts should be consulted for more details.

FDA pregnancy category Not Assigned: The FDA has changed the pregnancy labeling rule for prescription drug products to require labeling that includes a risk summary, a discussion of the data supporting that summary, and relevant information to help healthcare professionals make prescribing decisions and counsel women about the use of drugs during pregnancy. Pregnancy categories A, B, C, D, and X are being eliminated.

Breastfeeding Warnings for Tirzepatide

The benefit should outweigh the risk.

According to some authorities: The decision to discontinue breastfeeding or discontinue the drug should be made considering the importance of the drug to the mother.

- **Excreted in human milk:** Unknown;
- **Excreted in animal milk:** Unknown.

Comments

The benefits of breastfeeding for development and health should be considered, as well as the clinical need of the mother for this medication.

The effects on breastfeeding are unknown; possible side effects in the breastfed child due to this medication or the mother's underlying condition should be considered.

It is expected that the amount of this medication in breast milk or absorbed by the breastfed child will be low due to the high molecular weight of this medication and its likely partial destruction within the infant gastrointestinal tract.

Drug Interaction: What are the effects of taking Tirzepatide with other medications?

Pharmacokinetic Drug Interactions In Vitro and Other Pharmacokinetic Studies

Pharmacokinetic Drug Interactions In Vitro and Other Pharmacokinetic Studies

Tirzepatide delays gastric emptying and therefore has the potential to affect the absorption of orally administered medications taken concurrently. Based on physiologically-based pharmacokinetic models, treatment with Tirzepatide is not expected to have a clinically significant impact on orally administered medications (i.e., atorvastatin, digoxin, ethinyl estradiol, lisinopril, metformin, metoprolol, norelgestromin, acetaminophen, sitagliptin, and warfarin). No dose adjustment of concomitantly administered oral medications is necessary.

Tell your doctor and pharmacist about any prescription and over-the-counter medications, vitamins, nutritional supplements, and herbal products you plan to take or are taking. They may interact with Tirzepatide, and your doctor may need to adjust your medication doses or monitor you closely for side effects.

Birth control pills may not work as well while receiving this medication. Your doctor may suggest that you use another form of birth control for 4 weeks after starting Tirzepatide and for 4 weeks after each dose change.

Taking Tirzepatide with other medications for diabetes, such as sulfonylureas or insulin, may increase the risk of hypoglycemia. Discuss with your doctor and pharmacist about low blood sugar and how to manage it.

This list is not complete. Many other medications may interact with Tirzepatide, including prescription and over-the-counter medications, vitamins, and herbal products. To check for interactions with this medication, click the link below.

What precautions should I take when using Tirzepatide?

Before using Tirzepatide:

Inform your doctor and pharmacist if you are allergic to tirzepatide, any other medications, or any of the ingredients in this medication. A list of the ingredients in this medication can be found at the bottom of this page.

Tell your doctor if you have or have had kidney or pancreatic disease, a history of diabetic retinopathy, or any stomach problems, such as difficulty digesting food.

Notify your doctor if you plan to become pregnant, are pregnant, or are breastfeeding. If you become pregnant while taking this medication, you should inform your doctor.

For pregnancy and breastfeeding warnings with Tirzepatide, read more in the Risks section.

What is the action of the substance in Tirzepatide?

Pharmaceutical Technology Data

Characterization, Quality Control, and Stability of the Active Pharmaceutical Ingredient (API)

To verify the structure and other characteristics of the API, the primary structure was elucidated using techniques such as LC-MS, mass spectrometry, and peptide mapping analysis. The secondary structure was characterized using circular dichroism and FT-IR. The tertiary structure was characterized using CD spectroscopy, and the quaternary/association state was characterized using multi-angle static light scattering (MALS).

The quality control of the API meets internal specifications for tests of description, identification, bioidentity, assay, purity, impurities, deamidation, unspecified higher molecular species, residual solvents, water content, bacterial endotoxins, and microbiological analysis.

The tests, specifications, and analytical methods of quality control were deemed adequate to ensure the quality of the API.

The validations of the analytical methods of the API were performed and considered satisfactory, in line with the current standard.

Regarding isomerism, the drug exhibits spatial isomerism, and control of the isomers was demonstrated.

Regarding polymorphism, the polymorphic form of the API is amorphous; no crystalline forms were identified.

The stability data presented suggest a provisional shelf life of 24 months for the product with the storage statement:

- “Store at -25 °C to -10 °C.”
- As for light sensitivity, the active ingredient is photostable.

Drug Manufacturing Process and In-Process Controls

The company presented production and quality control data for batches that adequately demonstrated the consistency of the manufacturing process.

Quality Control of the Finished Product

The quality control of the medication meets internal specifications for tests of description, color, clarity, bacterial endotoxins, sterility, pH, osmolality, particulate matter, syringe functionality, identity, assay, purity, impurities, and high molecular weight species.

The tests, specifications, and methods of quality control were deemed adequate to ensure the quality of the medication.

The validations of the analytical methods of the medication were performed and considered satisfactory, in line with the current standard.

Stability and Compatibility of the Medication

The product is packaged in a 1 mL Type I transparent glass syringe with a fitted needle, capped with an elastomeric plunger and a rigid needle shield.

The data from the accelerated and long-term stability studies supported the shelf life for the product of 24 months under refrigeration (2 to 8°C). Protect from light. The data also support that the product can be stored outside refrigeration at temperatures below 30°C for up to 21 days.

The photostability study data confirm that the product in the syringe within the carton is photostable.

Safety and Efficacy Data

Mechanism of Action

Tirzepatide is highly selective for human GIP and GLP-1 receptors, for which it exhibits high affinity. The activity of Tirzepatide on the GIP receptor is similar to that of the natural GIP hormone. The activity of Tirzepatide on the GLP-1 receptor is less than that of the natural GLP-1 hormone.

Tirzepatide increases the sensitivity of β -cells to glucose, enhancing first and second-phase insulin secretion and reducing glucagon levels, both in a glucose-dependent manner. Tirzepatide improves insulin sensitivity, delays gastric emptying (an effect that diminishes over time), and reduces food intake.

Non-Clinical Studies

Pharmacology

Tirzepatide is a long-acting agonist of GIP and GLP-1 receptors. It is a 39-amino acid peptide with a 20-carbon fatty acid fragment that allows for albumin binding and extends the half-life. Tirzepatide improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through various mechanisms.

Tirzepatide 15 mg increased first and second-phase insulin secretion rates by 466% and 302%, respectively.

Tirzepatide 15 mg improved whole-body insulin sensitivity by 63%, measured by the M-value, a measure of glucose uptake by tissues. Tirzepatide reduces body weight in patients with type 2 diabetes, which may contribute to improved insulin sensitivity.

Tirzepatide 15 mg reduced fasting glucagon concentration by 28% and the area under the curve (AUC) of glucagon after a mixed meal by 43%.

Tirzepatide delays gastric emptying, which may reduce the rate of glucose absorption after meals and may lead to a beneficial effect on postprandial glycemia. Tirzepatide slows postprandial glucose absorption, reducing postprandial glucose levels. The delay is greater after the first dose and diminishes over time.

Pharmacokinetics

Absorption

After administration, the maximum concentration of Tirzepatide is reached between 8 and 72 hours. Steady-state exposure is achieved after 4 weeks of once-weekly administration. Exposure to Tirzepatide increases proportionally with the dose. Similar exposure was obtained with subcutaneous administration of Tirzepatide in the abdomen, thigh, or arm. The absolute bioavailability of subcutaneous Tirzepatide was 80%.

Distribution

The average apparent volume of distribution at steady state of Tirzepatide after subcutaneous administration in patients with type 2 diabetes is approximately 10.3 L. Tirzepatide exhibits high binding to plasma albumin (99.06%).

Metabolism

Tirzepatide is metabolized by proteolytic cleavage of the peptide backbone, beta-oxidation of the 20-carbon fatty acid fragment, and amide hydrolysis.

Elimination

The average population clearance of Tirzepatide is approximately 0.06 L/h, with a half-life of approximately 5 days, allowing for once-weekly administration.

Excretion

Tirzepatide is eliminated by metabolism. The primary routes of excretion for Tirzepatide metabolites are urine and feces. No intact Tirzepatide is observed in urine or feces.

Clinical Studies

Clinical Efficacy Analysis

Introduction

The safety and efficacy of Tirzepatide were evaluated in five global, randomized, controlled phase 3 studies (SURPASS 1-5), with the primary objective of measuring glycemic efficacy in 6,263 patients with type 2 diabetes (4,199 treated with Tirzepatide). Secondary objectives included weight loss, fasting

glucose, and the proportion of patients achieving the target hemoglobin A1c (HbA1c). All five phase 3 studies evaluated Tirzepatide at 5 mg, 10 mg, and 15 mg. All patients treated with Tirzepatide started at 2.5 mg for 4 weeks. The Tirzepatide dose was then increased by 2.5 mg every 4 weeks until the designated dose was reached. In all studies, treatment with Tirzepatide demonstrated sustained, statistically, and clinically significant reductions in HbA1c and body weight compared to baseline when compared to placebo or control treatment (semaglutide, degludec insulin, or glargine insulin) for up to 1 year. In one study, these effects were maintained for up to 2 years. The results of the phase 3 studies are presented below based on the modified intent-to-treat (mITT) population, which consists of all randomly selected patients who were exposed to at least one dose of the study treatment, excluding patients who discontinued treatment due to inadvertent recruitment. The analysis aligned with the efficacy estimate for a longitudinal continuous variable employed a mixed model for repeated measures.

Conclusions on Benefits and Risks

The U.S. Food & Drug Administration (FDA) is clear in concluding that the benefits of marketing Tirzepatide outweigh its risks, as described in Item 1 (Risk-Benefit Assessment and Discussion of Substantial Evidence of Efficacy) of the Summary Review Document, issued at the time of marketing authorization. Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion that affects over 30 million Americans.

The complications of hyperglycemia include an increased risk of microvascular complications (neuropathy, nephropathy, retinopathy) and macrovascular complications (myocardial infarction, stroke) and premature mortality. The overall goal of T2DM treatment is to achieve and maintain glycemic control to prevent these complications. Although there are 12 classes of FDA-approved antidiabetic therapies, many adults with T2DM do not reach glycemic targets. The Diabetes Control and Complications Trial determined that intensive glycemic control effectively delays the onset and slows the progression of diabetic retinopathy (including vision-threatening lesions), nephropathy, and neuropathy in patients with diabetes mellitus by a range of 35% to over 70%. Based on the DCCT, HbA1c is a validated surrogate endpoint for reducing microvascular risk in clinical trials for antihyperglycemic medications. Tirzepatide is the first dual receptor of glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist. The

applicant presented 19 clinical studies, including two phase 2 clinical trials (GPGB, GPGF), five randomized, double-blind, placebo-controlled or active comparator-controlled phase 3 clinical trials (SURPASS-1 (GPGK), SURPASS-2 (GPGL), SURPASS-3 (GPGH), SURPASS-4 (GPGM), and SURPASS-5 (GPGI)), two studies conducted in Japan (GPGO, GPGP), and ten other bio-pharmaceutical and clinical pharmacology studies. Five phase 3 studies met the criteria for adequate and well-controlled studies (21 CFR 314.126) and support the approval of Tirzepatide, demonstrating substantial evidence of efficacy. Tirzepatide was evaluated at three different doses (5, 10, and 15 mg) and administered as monotherapy; in combination with metformin, sulfonylureas, and sodium-glucose co-transporter-2 (SGLT-2) inhibitors; or in combination with basal insulin, with or without metformin. Compared to placebo, semaglutide 1 mg, degludec insulin, and glargine insulin, at all dosage levels, Tirzepatide demonstrated a statistically superior effect on the primary efficacy endpoint of change from baseline in hemoglobin A1c (HbA1c) at week 40 or week 52. Throughout the phase 3 studies, each reduction in HbA1c subtracted from the comparator was considered clinically significant (-0.41% to -1.64%), except for the 5 mg Tirzepatide arm compared to the 1 mg semaglutide arm (reduction of comparator subtraction of 0.16%, 95% CI: -0.29, -0.04). Sensitivity analyses were consistent with the results of the primary analyses. Subgroup analyses suggested that efficacy was not affected by age category, sex, race, or region. The results of the main secondary endpoints (including change in weight from baseline, change in fasting glucose from baseline, and incidence of HbA1c < 7% at Week 40 or 52) also showed favorable results and provided supportive evidence of efficacy. In fact, the study results showed statistically superior weight loss at week 40 with Tirzepatide compared to a GLP-1 receptor agonist, semaglutide 1 mg, at each dose level (1.9, 3.6, and 5.5 kg with Tirzepatide 5, 10, and 15 mg, respectively).

The safety profile characterized by the pre-marketing safety database, containing 5,415 patients in phases 2 and 3 exposed to Tirzepatide and 4,821 patients with at least 24 weeks of exposure, is consistent with other products with GLP-1 receptor activity. In SURPASS-2 (GPGL) comparing Tirzepatide with another GLP-1 receptor agonist (RA) (semaglutide 1 mg), individuals treated with Tirzepatide experienced more treatment interruptions due to adverse events (7.7% in the Tirzepatide group versus 4.1% in the semaglutide group), mainly due to gastrointestinal (GI) events (nausea, vomiting, diarrhea) with a greater difference at higher doses of Tirzepatide. In clinical studies, an imbalance in pancreatitis was observed with 14 events of acute pancreatitis in

13 patients treated with Tirzepatide (0.23 patients per 100 years of exposure) versus 3 events in 3 patients treated with the GLP-1 RA comparator (0.11 patients per 100 years of exposure). Six of these events in patients treated with Tirzepatide were serious adverse events, compared to 3 non-serious events in individuals treated with the comparator. Tirzepatide was associated with gastrointestinal adverse events, including nausea, diarrhea, decreased appetite, dyspepsia, vomiting, constipation, and abdominal pain in a dose-related manner. Tirzepatide was also associated with hypoglycemia when used concomitantly with insulin secretagogues or insulin and associated with injection site reactions and hypersensitivity reactions. However, in clinical trials comparing Tirzepatide with placebo, semaglutide, degludec insulin, or glargine insulin, patients randomized to treatment with Tirzepatide did not show an increased risk of hypoglycemia compared to patients randomized to treatment with the comparators. Tirzepatide also carries a boxed warning for thyroid C-cell tumors due to safety signals observed in non-clinical carcinogenicity studies.

Except for adverse reactions shared by GLP-1 receptor agonists (pancreatitis, gastrointestinal disorders, hypersensitivity reactions, and injection site reactions), numerical imbalances that were interpretable and clinically significant were not observed for other adverse events of special interest evaluated in the pre-marketing safety database. Additionally, no safety signals requiring post-marketing follow-up were identified. The product labeling for Tirzepatide will list the following risks in the Warnings and Precautions section: pancreatitis, hypoglycemia with concomitant insulin or insulin secretagogue, hypersensitivity reactions, acute kidney injury (AKI), severe gastrointestinal disease, complications of diabetic retinopathy in patients with a history of diabetic retinopathy, and acute gallbladder disease. The risk of AKI is included in the Tirzepatide labeling based on post-marketing reports of acute kidney injury related to severe gastrointestinal adverse reactions with the use of GLP-1 RA products. Thus, the labeling for most GLP-1 RAs encourages prescribers to monitor renal function in patients with or without renal insufficiency if they experience severe gastrointestinal adverse reactions. Additionally, the short-term risk of complications from diabetic retinopathy, hypothetically related to a rapid large reduction in HbA1c, is included in Tirzepatide labeling based on findings from clinical trials with other GLP-1 RAs. However, improved glycemic control should reduce the long-term risk of retinopathy. Finally, the risk of acute gallbladder events is included in Tirzepatide labeling in conjunction with the recent class labeling required by the FDA for GLP-1 RAs, based on

evidence from spontaneous adverse event reports and published case reports. This decision was supported by the finding of a higher number of individuals treated with Tirzepatide experiencing acute gallbladder events in phase 3 clinical trials.

In summary, Tirzepatide effectively reduces HbA1c and is expected to result in a reduced long-term risk of microvascular disease, preventing blindness, renal failure requiring dialysis, and amputation due to neuropathy. Additionally, Tirzepatide appears to provide superior glycemic control compared to some other available therapies, including semaglutide insulin 1 mg, degludec insulin, and glargine insulin. Another notable benefit of this drug is the favorable change in body weight (weight loss), as overweight and obesity contribute to the pathophysiology of T2DM. The adverse reaction profile is similar to that of marketed GLP-1 RAs, and due to the prevalent use of this class of medications, it is expected to be well accepted by patients with diabetes. The most common adverse reactions are related to gastrointestinal tolerability and decreased appetite. At the highest dose of 15 mg, 6.6% of patients discontinued Tirzepatide due to gastrointestinal adverse events. These adverse reactions are easily identifiable by patients who may choose to discontinue therapy without residual harm and it is expected that the dose will be clinically titrated according to tolerability and glycemic control needs. Serious potential harms include pancreatitis and acute cholecystitis, but these were rare and do not outweigh the anticipated benefits. The identified safety concerns can be addressed through labeling and routine pharmacovigilance. Additionally, two post-marketing safety studies (PMRs) will be conducted to monitor the potential risk of thyroid cancer and assess whether Tirzepatide is present in human breast milk.

The risk-benefit profile is favorable and supports the FDA's approval of Tirzepatide for the proposed indication "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

What are the ingredients of Tirzepatide?

Active Ingredient: Tirzepatide

Mounjaro Inactive Ingredients: Sodium chloride, disodium phosphate heptahydrate, and water for injection. Hydrochloric acid and/or sodium hydroxide solution may have been added to adjust the pH.

Consulted Sources

- Public Opinion on the Medication Mounjaro:
<https://consultas.anvisa.gov.br/#/pareceres/q/?nomeProduto=MOUNJARO>.
- (2023) "Product Information. Mounjaro (tirzepatide)." Eli Lilly and Company Ltd.
- (2023) "Product Information. Mounjaro (tirzepatide)." Lilly, Eli and Company.
- (2023) "Product Information. Mounjaro (tirzepatide)." Eli Lilly Australia Pty Ltd.
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- (2023) "Product Information. Mounjaro (tirzepatide)." Eli Lilly and Company Ltd.
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- (2023) "Product Information. Mounjaro (tirzepatide)." Eli Lilly and Company Ltd.
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More Information

Always consult your healthcare professional to ensure that the information displayed on this page applies to your personal circumstances.

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