Novo-Iela

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

TIRZEPATIDE (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 TIRZEPATIDE 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).**
- **TIRZEPATIDE is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

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

TIRZEPATIDE 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: 10 mg, 30 mg per 3 mL in multi-dose cartridges (3)

Injection: 10 mg, 30 mg per 3 mL in multi-dose Auto-injector Pen (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 TIRZEPATIDE (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:* Hypersensitivity reactions have been reported. Discontinue TIRZEPATIDE if suspected. (5.4)
- *Acute Kidney Injury:* Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. (5.5)
- *Severe Gastrointestinal Disease:* Use may be associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients. (5.6)
- *Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy:* Has not been studied in patients with non- proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor patients with a history of diabetic retinopathy for progression. (5.7)
- *Acute Gallbladder Disease:* Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow- up are indicated. (5.8)

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

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

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

TIRZEPATIDE 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)

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 TIRZEPATIDE 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 *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **TIRZEPATIDE 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 TIRZEPATIDE 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 TIRZEPATIDE *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

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

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 INSULIN SYRINGE & CATRIDGE DOSAGE

10mg/3ml Cartridge	**Dose**	**Weekly dose**	**Units to Insulin syringe**
Starting Weeks	Week 1–4	2,5 mg	75 units (or 38 units 2x per week (EG: Mon, Thurs)
Maintenance Phase 1	Week 5–8	5 mg	150 units (or 75 units 2x per week (EG: Mon, Thurs)
• It is recommended to move to the 30mg/3ml variant for less volume of injection fluid. • The below dosages are only applicable should your doctor prescribe a higher dosage.			

30mg/3ml Cartridge	**Dose**	**Weekly dose**	**Units to inject**
Starting Weeks	Week 1–4	2,5 mg	25 units once per week
Maintenance Phase 1	Week 5–8	5 mg	50 units once per week
Maintenance Phase 2	Week 9–12	7,5 mg	75 units (or 38 units 2x per week (EG: Mon, Thurs)
Maintenance Phase 3	Week 13–16	10 mg	100 units (or 50 units 2x per week (EG: Mon, Thurs)
Maintenance Phase 4	Week 17-20	12,5 mg	125 units (or 63 units 2x per week (EG: Mon, Thurs)
Maintenance Phase 5	Week 21+	15 mg	150 units (or 75 units 2x per week (EG: Mon, Thurs)

2.2 AUTO-INJECTOR PEN DOSAGE

10 mg/3 ml Auto-injector Pen	**Weekly Dose**	**Clicks on Pen**
Starting Dose	2.5 mg	75 clicks (or 38 clicks 2x per week (EG: Mon, Thurs)
Increase after 4 weeks	5 mg	150 clicks (or 75 clicks 2x per week (EG: Mon, Thurs)
Subsequent Increases*	+2.5 mg	Increase in 75-click increments
Maximum Dose	15 mg	450 clicks (once weekly)

Recommendation: Switch to the 30 mg/3 ml Auto-injector Pen for enhanced glycemic control.

30 mg/3 ml Auto-injector Pen	**Weekly Dose**	**Clicks on Pen**
Starting Dose	2.5 mg	25 clicks (once weekly)
Increase after 4 weeks	5 mg	50 clicks (once weekly)
Subsequent Increases*	+2.5 mg	Increase in 25-click increments
Intermediate Doses	7.5 mg / 10 mg / 12.5 mg	75 / 100 / 125 clicks
Maximum Dose	15 mg	150 clicks (once weekly)

Notes:

- *For additional glycemic control*, increase by 2.5 mg every 4 weeks as required.
- **Split Dosage Option:** Dosages may be administered as a single weekly injection or split into two injections.
- **Initiation Dosage:** The 2.5 mg starting dose is for initial treatment only, not for sustained glycemic control.

Important Administration Instructions

- Administer TIRZEPATIDE once weekly, any time of day, with or without meals.
- Inject TIRZEPATIDE subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.
- Inspect TIRZEPATIDE visually before use. It should appear clear and colorless to slightly yellow. Do not use TIRZEPATIDE if particulate matter or discoloration is seen.
- When using TIRZEPATIDE with insulin, administer as separate injections and never mix. It is acceptable to inject TIRZEPATIDE 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 available in pre-filled single-dose of the following strengths:

- Cartridge 10 mg/3 mL
- Cartridge 30 mg/3 mL
- Auto-Injector Pen 10 mg/3 mL
- Auto-Injector Pen 30 mg/3 mL

4 CONTRAINDICATIONS

TIRZEPATIDE 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 TIRZEPATIDE *[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 TIRZEPATIDE 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.

TIRZEPATIDE 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 TIRZEPATIDE 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 TIRZEPATIDE. 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 TIRZEPATIDE-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). TIRZEPATIDE 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 TIRZEPATIDE.

After initiation of TIRZEPATIDE, 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 TIRZEPATIDE and initiate appropriate management.

5.3 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients receiving TIRZEPATIDE 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

Hypersensitivity reactions have been reported with TIRZEPATIDE in clinical trials (e.g., urticaria and eczema) and were sometimes severe. If hypersensitivity reactions occur, discontinue use of TIRZEPATIDE; 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 TIRZEPATIDE *[see Contraindications (4)]*.

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 TIRZEPATIDE.

5.5 Acute Kidney Injury

TIRZEPATIDE 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 post marketing 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 TIRZEPATIDE in patients with renal impairment reporting severe gastrointestinal adverse reactions.

5.6 Severe Gastrointestinal Disease

Use of TIRZEPATIDE has been associated with gastrointestinal adverse reactions, sometimes severe *[see Adverse Reactions 6.1]*. TIRZEPATIDE 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. TIRZEPATIDE 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 post marketing.

In TIRZEPATIDE placebo-controlled clinical trials, acute gallbladder disease (cholelithiasis, biliary colic, and cholecystectomy) was reported by 0.6% of TIRZEPATIDE-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 *[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 TIRZEPATIDE and a mean duration of exposure to TIRZEPATIDE 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 m^2 in 53%, 60 to 90 mL/min/1.73 m^2 in 39%, 45 to 60 mL/min/1.73 m^2 in 7%, and 30 to 45 mL/min/1.73 m^2 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 TIRZEPATIDE 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 TIRZEPATIDE 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 m^2 in 52%, 60 to 90 mL/min/1.73 m^2 in 40%, 45 to 60 mL/min/1.73 m^2 in 6%, and 30 to 45 mL/min/1.73 m^2 in 1% of patients.

Common Adverse Reactions

Table 1 shows common adverse reactions, not including hypoglycemia, associated with the use of TIRZEPATIDE in the pool of placebo-controlled trials. These adverse reactions occurred more commonly on TIRZEPATIDE than on placebo and occurred in at least 5% of patients treated with TIRZEPATIDE.

Table 1: Adverse Reactions in Pool of Placebo-Controlled Trials Reported in ≥5% of TIRZEPATIDE-treated Adult Patients with Type 2 Diabetes Mellitus

Adverse Reaction	Placebo (N=235) %	TIRZEPATIDE 5 mg (N=237) %	TIRZEPATIDE 10 mg (N=240) %	TIRZEPATIDE 15 mg (N=241) %
Nausea	4	12	15	18
Diarrhea	9	12	13	17
Decreased Appetite	1	5	10	11
Vomiting	2	5	5	9
Constipation	1	6	6	7
Dyspepsia	3	8	8	5
Abdominal Pain	4	6	5	5

Note: Percentages reflect the number of patients who reported at least 1 occurrence of the adverse reaction.

In the pool of seven clinical trials, the types and frequency of common adverse reactions, not including hypoglycemia, were similar to those listed in Table 1.

Gastrointestinal Adverse Reactions

In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving TIRZEPATIDE than placebo (placebo 20.4%, TIRZEPATIDE 5 mg 37.1%, TIRZEPATIDE 10 mg 39.6%, TIRZEPATIDE 15 mg 43.6%). More patients receiving TIRZEPATIDE 5 mg (3.0%), TIRZEPATIDE 10 mg (5.4%), and TIRZEPATIDE 15 mg (6.6%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.4%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation and decreased over time.

The following gastrointestinal adverse reactions were reported more frequently in TIRZEPATIDE-treated patients than placebo-treated patients (frequencies listed, respectively, as: placebo; 5 mg; 10 mg; 15 mg): eructation (0.4%, 3.0%, 2.5%, 3.3%), flatulence (0%, 1.3%, 2.5%, 2.9%), gastroesophageal reflux disease (0.4%, 1.7%, 2.5%, 1.7%), abdominal distension (0.4%, 0.4%, 2.9%, 0.8%). Other Adverse Reactions

Hypoglycemia

Table 2 summarizes the incidence of hypoglycemic events in the placebo-controlled trials.

Table 2: Hypoglycemia Adverse Reactions in Placebo-Controlled Trials in Adult Patients with Type 2 Diabetes Mellitus

	Placebo %	TIRZEPATIDE 5 mg %	TIRZEPATIDE 10 mg %	TIRZEPATIDE 15 mg %
Monotherapy				
(40 weeks)*	N=115	N=121	N=119	N=120
Blood glucose <54 mg/dL	1	0	0	0

Severe hypoglycemia**	0	0	0	0
Add-on to Basal Insulin with or without Metformin				
(40 weeks)*	N=120	N=116	N=119	N=120
Blood glucose <54 mg/dL	13	16	19	14
Severe hypoglycemia**	0	0	2	1

* Reflects the study treatment period. Data include events occurring during 4 weeks of treatment-free safety follow up. Events after introduction of a new glucose-lowering treatment are excluded.

** Episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Hypoglycemia was more frequent when TIRZEPATIDE was used in combination with a sulfonylurea *[see Clinical Studies (14)]*. In a clinical trial up to 104 weeks of treatment, when administered with a sulfonylurea, hypoglycemia (glucose level <54 mg/dL) occurred in 13.8%, 9.9%, and 12.8%, and severe hypoglycemia occurred in 0.5%, 0%, and 0.6% of patients treated with TIRZEPATIDE 5 mg, 10 mg, and 15 mg, respectively.

Heart Rate Increase

In the pool of placebo-controlled trials, treatment with TIRZEPATIDE resulted in a mean increase in heart rate of 2 to 4 beats per minute compared to a mean increase of 1 beat per minute in placebo-treated patients. Episodes of sinus tachycardia, associated with a concomitant increase from baseline in heart rate of ≥15 beats per minute, also were reported in 4.3%, 4.6%, 5.9% and 10% of subjects treated with placebo, TIRZEPATIDE 5 mg, 10 mg, and 15 mg, respectively. For patients enrolled in Japan, these episodes were reported in 7% (3/43), 7.1% (3/42), 9.3% (4/43), and 23% (10/43) of patients treated with placebo, TIRZEPATIDE 5 mg, 10 mg, and 15 mg, respectively. The clinical relevance of heart rate increases is uncertain.

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with TIRZEPATIDE in the pool of placebo-controlled trials, sometimes severe (e.g., urticaria and eczema); hypersensitivity reactions were reported in 3.2% of TIRZEPATIDE-treated patients compared to 1.7% of placebo-treated patients.

In the pool of seven clinical trials, hypersensitivity reactions occurred in 106/2,570 (4.1%) of TIRZEPATIDE-treated patients with anti-tirzepatide antibodies and in 73/2,455 (3.0%) of TIRZEPATIDE-treated patients who did not develop anti- tirzepatide antibodies *[see Clinical Pharmacology (12.6)]*.

Injection Site Reactions

In the pool of placebo-controlled trials, injection site reactions were reported in 3.2% of TIRZEPATIDE-treated patients compared to 0.4% of placebo-treated patients.

In the pool of seven clinical trials, injection site reactions occurred in 119/2,570 (4.6%) of TIRZEPATIDE-treated patients with anti-tirzepatide antibodies and in 18/2,455 (0.7%) of TIRZEPATIDE-treated patients who did not develop anti- tirzepatide antibodies *[see Clinical Pharmacology (12.6)]*.

Acute Gallbladder Disease

In the pool of placebo-controlled clinical trials, acute gallbladder disease (cholelithiasis, biliary colic and cholecystectomy) was reported by 0.6% of TIRZEPATIDE-treated patients and 0% of placebo-treated patients.

Laboratory Abnormalities

Amylase and Lipase Increase

In the pool of placebo-controlled clinical trials, treatment with TIRZEPATIDE resulted in mean increases from baseline in serum pancreatic amylase concentrations of 33% to 38% and serum lipase concentrations of 31% to 42%. Placebo- treated patients had a mean increase from baseline in pancreatic amylase of 4% and no changes were observed in lipase. The clinical significance of elevations in lipase or amylase with TIRZEPATIDE is unknown in the absence of other signs and symptoms of pancreatitis.

7 DRUG INTERACTIONS

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

When initiating TIRZEPATIDE, 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

TIRZEPATIDE 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 TIRZEPATIDE.

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 TIRZEPATIDE.

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 TIRZEPATIDE. 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 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with TIRZEPATIDE 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. TIRZEPATIDE 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 TIRZEPATIDE and any potential adverse effects on the breastfed infant from TIRZEPATIDE or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Use of TIRZEPATIDE 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 TIRZEPATIDE *[see Drug Interactions (7.2) and Clinical Pharmacology (12.2, 12.3)]*.

8.4 Pediatric Use

Safety and effectiveness of TIRZEPATIDE have not been established in pediatric patients (younger than 18 years of age).

8.5 Geriatric Use

In the pool of seven clinical trials, 1539 (30.1%) TIRZEPATIDE-treated patients were 65 years of age or older, and 212 (4.1%) TIRZEPATIDE-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 TIRZEPATIDE 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 TIRZEPATIDE in patients with renal impairment reporting severe adverse gastrointestinal reactions *[see Warnings and Precautions (5.5)]*.

8.7 Hepatic Impairment

No dosage adjustment of TIRZEPATIDE 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)]*.

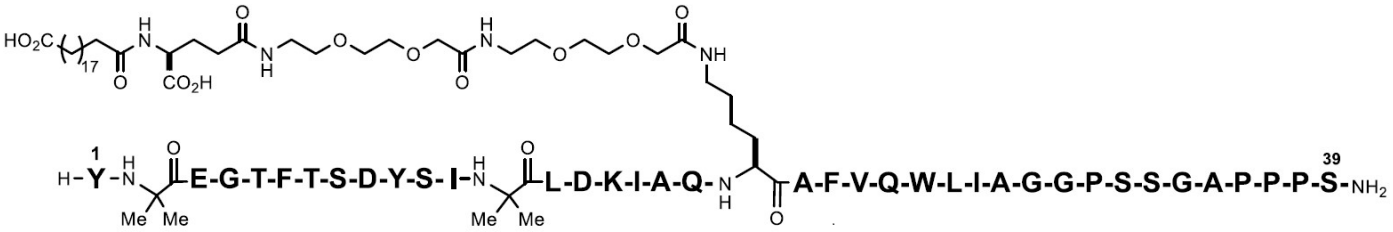
9 OVERDOSAGE

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.

10 DESCRIPTION

TIRZEPATIDE (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 $C_{225}H_{348}N_{48}O_{68}$.

Structural formula:



TIRZEPATIDE is a clear, colorless to slightly yellow, sterile, preservative-free solution for subcutaneous use. Each Multi-dose Cartridge and Auto-injector Pen contains a 3 ml solution of 10 mg and 30 mg of tirzepatide and the following excipients: sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection.

Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. TIRZEPATIDE has a pH of 6.5 – 7.5.

11 CLINICAL PHARMACOLOGY

11.1 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 glucose- dependent manner.

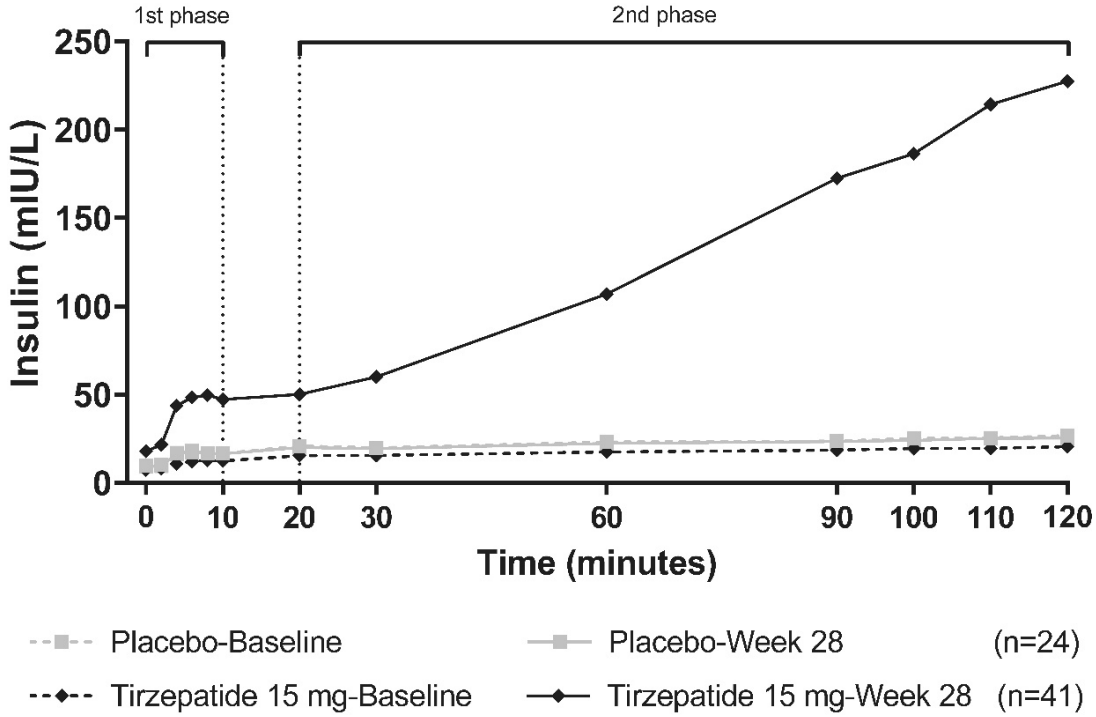
11.2 Pharmacodynamics

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. (Figure 1)

Figure 1: Mean insulin concentration at 0-120 minutes during hyperglycemic clamp at baseline and week 28



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.

11.3 Pharmacokinetics

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with type 2 diabetes mellitus. Steady- state 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.

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.

TIRZEPATIDE 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 (C_{max}) was reduced by 50%, and the median peak plasma concentration (t_{max}) occurred 1 hour later. After coadministration at week 4, there was no meaningful impact on acetaminophen C_{max} and t_{max}. Overall acetaminophen exposure (AUC_{0-24hr}) 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 C_{max} 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 t_{max} of 2.5 to 4.5 hours was observed.

11.4 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, including those of tirzepatide or of GLP-1 receptor agonist products.

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 TIRZEPATIDE-treated patients developed anti-tirzepatide antibodies. In these trials, anti-tirzepatide antibody formation in 34% and 14% of TIRZEPATIDE- treated patients showed cross-reactivity to native GIP or native GLP-1, respectively.

Of the 2,570 TIRZEPATIDE-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.

There was no identified clinically significant effect of anti-tirzepatide antibodies on pharmacokinetics or effectiveness of TIRZEPATIDE. More TIRZEPATIDE-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)]*.

12 NONCLINICAL TOXICOLOGY

12.1 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.

13 CLINICAL STUDIES

13.1 Overview of Clinical Studies

The effectiveness of TIRZEPATIDE 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, TIRZEPATIDE 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, TIRZEPATIDE (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 TIRZEPATIDE produced a statistically significant reduction from baseline in HbA1c compared to placebo. The effectiveness of TIRZEPATIDE was not impacted by age, gender, race, ethnicity, region, or by baseline BMI, HbA1c, diabetes duration, or renal function.

13.2 Monotherapy Use of TIRZEPATIDE 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 TIRZEPATIDE 5 mg, TIRZEPATIDE 10 mg, TIRZEPATIDE 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/m^2. 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 TIRZEPATIDE 5 mg, 10 mg and 15 mg once weekly for 40 weeks resulted in a statistically significant reduction in HbA1c compared with placebo (see Table 3).

Table 3: Results at Week 40 in a Trial of TIRZEPATIDE as Monotherapy in Adult Patients with Type 2 Diabetes. Mellitus with Inadequate Glycemic Control with Diet and Exercise

	Placebo	TIRZEPATIDE 5 mg	TIRZEPATIDE 10 mg	TIRZEPATIDE 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	113	121	121	120
HbA1c (%)				
Baseline (mean)	8.1	8.0	7.9	7.9
Change at Week 40[b]	-0.1	-1.8	-1.7	-1.7
Difference from placebo[b] (95% CI)	--	-1.7[c] (-2.0, -1.4)	-1.6[c] (-1.9, -1.3)	-1.6[c] (-1.9, -1.3)
Patients (%) achieving HbA1c <7%[d]	23	82[c]	85[c]	78[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	155	154	153	154
Change at Week 40[b]	4	-40	-40	-39
Difference from placebo[b] (95% CI)	--	-43[c] (-55, -32)	-43[c] (-55, -32)	-42[c] (-54, -30)
Body Weight (kg)				
Baseline (mean)	84.5	87.0	86.2	85.5
Change at Week 40[b]	-1.0	-6.3	-7.0	-7.8
Difference from placebo[b] (95% CI)	--	-5.3[c] (-6.8, -3.9)	-6.0[c] (-7.4, -4.6)	-6.8[c] (-8.3, -5.4)

[a] The modified intent-to-treat population consists of all randomly assigned participants who were exposed to at least 1 dose of study drug. Patients who discontinued study treatment because they did not meet study enrollment criteria were excluded.

During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 25%, 2%, 3%, and 2% of patients randomized to placebo, TIRZEPATIDE 5 mg, 10 mg, and 15 mg, respectively. At Week 40 the HbA1c data were missing for 12%, 6%, 7%, and 14% of patients randomized to placebo, TIRZEPATIDE 5 mg, 10 mg, and 15 mg, respectively. Missing Week 40 data were imputed using placebo-based multiple imputation.

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] p<0.001 (two-sided) for superiority vs. placebo, adjusted for multiplicity.

[d] Analyzed using logistic regression adjusted for baseline value and other stratification factors.

14 HOW SUPPLIED/STORAGE AND HANDLING

14.1 How Supplied

- TIRZEPATIDE is a clear, colorless to slightly yellow solution available in pre-filled multi-dose cartridges as follows:

Total Strength per Total Volume	Contents
10 mg/3 mL	1 Multi-dose Cartridge
30 mg/3 mL	1 Multi-dose Cartridge
10 mg/3 mL	1 Multi -dose Auto-injector Pen, 4 insulin needles
30 mg/3 mL	1 Multi -dose Auto-injector Pen, 4 insulin needles

14.2 Storage and Handling

- Store TIRZEPATIDE in a refrigerator at 2°C to 8°C (36°F to 46°F).
- If needed, each single-dose Cartridge can be stored unrefrigerated at temperatures not to exceed 30ºC (86ºF) for up to 21 days.
- Do not freeze TIRZEPATIDE. Do not use TIRZEPATIDE if frozen.
- Store TIRZEPATIDE in the original carton to protect from light.

15 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 TIRZEPATIDE 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 TIRZEPATIDE 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 TIRZEPATIDE 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 hypersensitivity reactions have been reported with use of TIRZEPATIDE. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking TIRZEPATIDE and seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.4)]*.

Acute Kidney Injury

Advise patients treated with TIRZEPATIDE 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 TIRZEPATIDE *[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)]*.

Contraception

Use of TIRZEPATIDE 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 TIRZEPATIDE *[see Drug Interactions (7.2), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)].*

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)].*

Medication Guide TIRZEPATIDE
injection, for subcutaneous use

What is the most important information I should know about TIRZEPATIDE? TIRZEPATIDE may cause serious side effects, including:

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

What is TIRZEPATIDE?

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

Do not use TIRZEPATIDE if:

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

Before using TIRZEPATIDE, tell your healthcare provider about all of your medical conditions, **including if you:**

- have or have had problems with your pancreas or kidneys.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- have a history of diabetic retinopathy.
- are pregnant or plan to become pregnant. It is not known if TIRZEPATIDE will harm your unborn baby. Tell your healthcare provider if you become pregnant while using TIRZEPATIDE.
    - **Birth control pills by mouth may not work as well while using TIRZEPATIDE**. If you take birth control pills by mouth, your healthcare provider may recommend another type of birth control for 4 weeks after you start TIRZEPATIDE and for 4 weeks after each increase in your dose of TIRZEPATIDE. Talk to your healthcare provider about birth control methods that may be right for you while using TIRZEPATIDE.
- are breastfeeding or plan to breastfeed. It is not known if TIRZEPATIDE passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using TIRZEPATIDE.

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

Before using TIRZEPATIDE, tell your healthcare provider if you are taking other medicines to treat diabetes including insulin or sulfonylureas which could increase your risk of low blood sugar. Talk to your healthcare provider about low blood sugar and how to manage it.

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

How should I use TIRZEPATIDE?

- Read the **Instructions for Use** that comes with TIRZEPATIDE.
- Use TIRZEPATIDE exactly as your healthcare provider tells you to.
- TIRZEPATIDE is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm.
- **Use TIRZEPATIDE 1 time each week, at any time of the day.**
- You may change the day of the week you use TIRZEPATIDE as long as the time between the 2 doses is at least **3** days (72 hours).
- If you miss a dose of TIRZEPATIDE, take the missed dose 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 take your next dose on the regularly scheduled day. **Do not** take **2** doses of TIRZEPATIDE within **3** days of each other.
- TIRZEPATIDE may be taken with or without food.
- **Do not** mix insulin and TIRZEPATIDE together in the same injection.
- You may give an injection of TIRZEPATIDE and insulin in the same body area (such as your stomach area), but not right next to each other.
- Change (rotate) your injection site with each weekly injection. **Do not** use the same site for each injection.
- If you take too much TIRZEPATIDE, call your healthcare provider.

What are the possible side effects of TIRZEPATIDE? TIRZEPATIDE may cause serious side effects, including:

- See **"What is the most important information I should know about TIRZEPATIDE?"**
- **inflammation of your pancreas (pancreatitis).** Stop using TIRZEPATIDE and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you use TIRZEPATIDE with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. **Signs and symptoms of low blood sugar may include:**
  - dizziness or light-headedness
  - sweating
  - confusion or drowsiness
  - headache
  - blurred vision
  - slurred speech
  - shakiness
  - fast heartbeat
  - anxiety, irritability, or mood changes
  - hunger
  - weakness
  - feeling jittery
- **serious allergic reactions.** Stop using TIRZEPATIDE and get medical help right away if you have any symptoms of a serious allergic reaction including:
  - swelling of your face, lips, tongue or throat
  - problems breathing or swallowing
  - severe rash or itching
  - fainting or feeling dizzy
  - very rapid heartbeat
- **kidney problems (kidney failure).** In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse. It is important for you to drink fluids to help reduce your chance of dehydration.
- **severe stomach problems.** Stomach problems, sometimes severe, have been reported in people who use TIRZEPATIDE. Tell your healthcare provider if you have stomach problems that are severe or will not go away.
- **changes in vision.** Tell your healthcare provider if you have changes in vision during treatment with TIRZEPATIDE.
- **gallbladder problems.** Gallbladder problems have happened in some people who use TIRZEPATIDE. Tell your healthcare provider right away if you get symptoms of gallbladder problems which may include:
  - pain in your upper stomach (abdomen)
  - fever
  - yellowing of skin or eyes (jaundice)
  - clay-colored stools

The most common side effects of TIRZEPATIDE include:

- nausea
- diarrhea
- decreased appetite
- vomiting
- constipation
- indigestion
- stomach (abdominal) pain

Talk to your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of TIRZEPATIDE. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TIRZEPATIDE?

- Store TIRZEPATIDE in the refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Store TIRZEPATIDE in the original carton until use to protect it from light.
- If needed, each single-dose Cartridge can be stored at room temperature up to 86ºF (30ºC) for up to 21 days.
- Do not freeze TIRZEPATIDE. Do not use TIRZEPATIDE if frozen.

Keep TIRZEPATIDE and all medicines out of the reach of children.
General information about the safe and effective use of TIRZEPATIDE. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TIRZEPATIDE for a condition for which it was not prescribed. Do not give TIRZEPATIDE to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TIRZEPATIDE that is written for health professionals.
What are the ingredients in TIRZEPATIDE? **Active ingredient:** tirzepatide **Inactive ingredients:** sodium chloride, sodium phosphate dibasic heptahydrate, and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH.

Catridge

Auto-injector Pen

Instructions for use of the Auto-injector Pen
Before you start using the Novo-lela® one-single injection pen please read these instructions carefully and consult your doctor.
The Auto-injector Pen is designed for use with single-use needles, Novo-lela® is compatible with any injection pens needles.

The package contains:
• Novo-lela® injection pen (Fig. 1)
• 4 needles (depending on the package, purchased separately if not available)
• Package insert scan QR code
• Patient information

Example of a Novo-lela® Auto injection pen

Please note that the size and color of the label on the syringe pen may differ from the sample shown in these pictures.

These instructions apply to all Novo-lela® Auto injection pens. (Fig. 1).

Fig. 1

1. Before use

Take the pen from the refrigerator. After removing from the refrigerator, keep the pen at room temperature for at least 30 minutes before use.

Check the label and expiration date to ensure that the product is suitable for use (Fig. 2).

Fig. 2

Remove the cap and check the presence of the medicine through the window. Make sure that the Novo-lela® in the injection pen is transparent, colourless or with a slightly brownish tint (Fig. 3).

Fig. 3

2. Preparing and inserting the needle

Take a new pen needle, remove the protective sticker (Fig. 4).

• Before removing the protective sticker, make sure that the protective sticker and the cap on the needle are completely closed, avoid using non-sterile needles.

• You should use a new needle, as needles are disposable and cannot be reused. Reuse can lead to infection and the inability to administer the required dose of the drug.

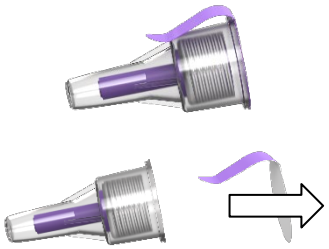


Fig.4

Align the outer needle cap with the pen and install it as shown in (Fig. 5).

Fig.5

Align the outer cap of the needle with the bottom towards the thread of the syringe pen and screw the needle directly onto the cartridge holder (Fig. 6, 7).

Fig.6

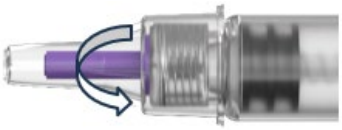


Fig.7

Remove the outer and then the inner needle caps (Fig. 8)

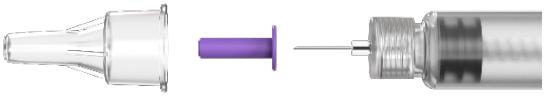


Fig.8

- Keep the outer needle cap so that it can be used after the injection.
- Discard the inner needle cap so that children do not eat it by mistake.
- Do not close the inner needle cap again to avoid accidental needle stick.

3. Removing air from the needle and checking its passableness

Turn the dose selector on the pen until the "□" symbol appears in the dose counter window and align it with the pointer (Fig. 9).

Fig 9

Hold the pen with the needle pointing upward, then press the trigger button until "0" appears in the dose counter window (Fig. 10, 11).

Fig.10

Fig. 11

Check if there are any drops on the tip of the needle. If there are no drops, repeat the air removal steps until drops appear on the tip of the needle (Fig. 12, 13).

Fig.12

Fig.13

- If drops do not appear after the air has been removed three times, it is possible that the needle of the syringe pen you are using is blocked. You should throw away this needle, replace it with a new one and repeat the steps described in point 3.
- It is permissible for there to be an air bubble in the drug solution visible in the window. This does not prevent the drug from being administered.

4. Injections

Select the site where you want to give the injection according to Fig. 15 and remove any clothing from the injection site.

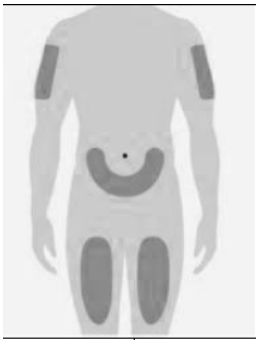


Fig.15

Insert the needle using the injection technique recommended by your doctor. Press the trigger button of the syringe pen (Fig. 16, 17).

Fig. 16

Fig. 17

Count 6-8 seconds after the dose counter window on the scale shows “0”. Then release the trigger button of the syringe pen and remove the needle from the skin (Fig. 18).

Fig. 18

- Removing the needle too early may prevent you from receiving the full dose of medication.
- Do not release the pen trigger until the dose indicator shows “0”. If the dose counter stops before the zero mark aligns with the pointer, this means that you have not received the required dose of medication.
- Please do not rely on the clicking sound to determine whether the injection is complete.

5. After injections

Place the outer needle cap on the table, then align the tip of the needle with the outer needle cap and insert it (Fig. 19).

Fig. 19

Once the needle enters the outer cap, gently push down on the outer cap until the needle is fully seated (Fig. 20, 21).

Fig.20

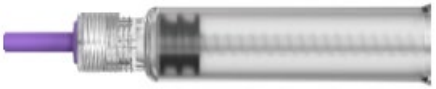


Fig. 21

Once the needle has entered the outer cap, gently press down on the outer cap until the needle is completely locked in place (Fig. 20, 21).

Fig. 22

Put the cap back on the pen and store it in a place protected from light (Fig. 23).

Fig. 23

- Remove the needle immediately after injection.
- Needles should be disposed of in accordance with the recommendations of health workers and sanitary and epidemiological standards.

WARNINGS:

- Do not freeze the pen.
- Avoid dropping the pen as it can break the inner cartridge and affect solutions stability.
- Do not place the pen in a high temperature or liquid environment.
- Do not attempt to refill the pen.
- Do not attempt to repair the pen.

Read this Instructions for Use and the Medication Guide before using your TIRZEPATIDE Cartridge and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

Talk to your healthcare provider about how to inject TIRZEPATIDE the right way.

- TIRZEPATIDE is a multi-dose prefilled Cartridge.
- TIRZEPATIDE is used 1 time each week unless dosage is split into two injections.
- Inject under the skin (subcutaneously) only.
- You or another person can inject into your stomach (abdomen) or thigh.
- Another person can inject into the back of your upper arm.

Storage and handling:

- Store your cartridge in the refrigerator between 36°F to 46°F (2°C to 8°C).
- You may store your Cartridge at room temperature up to 86°F (30°C) for up to 21 days.
- **Do not freeze your Cartridge.** If the Cartridge has been frozen, throw the Cartridge away and use a new Cartridge.
- Store your Cartridge in the original carton to protect your Cartridge from light.
- The Cartridge has glass parts. Handle it carefully. If you drop the Cartridge on a hard surface, **do not** use it. Use a new Cartridge for your injection.
- Keep your TIRZEPATIDE Cartridge and all medicines out of the reach of children.

Marketing Authorisation Holder and Manufacturer

Novo-lela
Product of Sweden

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www.novo-lela.com

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