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PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMOUNJARO®

tirzepatide injection

Solution, 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL, in a single-dose prefilled pen for subcutaneous use

Solution, 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL, in a single-dose vial for subcutaneous use

PrMOUNJARO® KwikPen®

tirzepatide injection

Solution, 2.5 mg/0.6 mL, 5 mg/0.6 mL, 7.5 mg/0.6 mL, 10 mg/0.6 mL, 12.5 mg/0.6 mL, and 15 mg/0.6 mL, in a multi-dose prefilled pen for subcutaneous use

Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist

Antihyperglycemic Agent

Eli Lilly Canada Inc.
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RECENT MAJOR LABEL CHANGES

2 Contraindications	09/2024
4 Dosage and Administration, 4.4 Administration	09/2024
7 Warnings and Precautions	09/2024

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MOUNJARO (tirzepatide injection) is indicated for once-weekly administration as an adjunct to diet and exercise to improve glycemic control for the treatment of adult patients with type 2 diabetes mellitus.

- As **monotherapy** when metformin is inappropriate due to contraindication or intolerance.
- In **combination with**:
  - metformin, or
  - metformin and a sulfonylurea (see 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS), or
  - metformin and a sodium-glucose cotransporter 2 inhibitor (SGLT2i), or
  - basal insulin with or without metformin (see 4.1 Dosing Considerations and 7 WARNINGS AND PRECAUTIONS).

Limitations of Use

MOUNJARO has not been studied in combination with short-acting, medium-acting, or dual formulation insulins.

MOUNJARO is not a substitute for insulin.

MOUNJARO should not be used in patients with type 1 diabetes mellitus (formerly known as insulin-dependent diabetes mellitus or IDDM).

MOUNJARO should not be used for the treatment of diabetic ketoacidosis.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of MOUNJARO have not been studied in pediatric patients. MOUNJARO is not indicated for use in pediatric patients.

1.2 Geriatrics

Geriatrics (≥65 years of age): No overall differences in safety or efficacy were observed in clinical trial patients ≥65 years of age compared to younger patients (see 4 DOSAGE AND ADMINISTRATION, 7.1.4 Geriatrics, and 10.3 Pharmacokinetics).

2 CONTRAINDICATIONS

MOUNJARO is contraindicated:

- in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient (including benzyl alcohol when using MOUNJARO KwikPen), or component of the container (see 7 WARNINGS AND PRECAUTIONS). (For a complete listing of the ingredients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- 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 7 WARNINGS AND PRECAUTIONS).
- during pregnancy or breast-feeding (see 7.1.1 Pregnant Women and 7.1.2 Breast-feeding).

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3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

RISK OF THYROID C-CELL TUMORS

- Tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and carcinomas) at clinically relevant exposures in male and female rats (see 16 NON-CLINICAL TOXICOLOGY). It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans. The human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (see 7 WARNINGS AND PRECAUTIONS).
- MOUNJARO is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS and 16 NON-CLINICAL TOXICOLOGY).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

An increased risk of hypoglycemia was seen with concomitant use of a sulfonylurea or basal insulin with MOUNJARO To reduce the risk of hypoglycemia, a reduction in the dose of insulin secretagogue or insulin should be considered when MOUNJARO is added to either of these existing therapies. In a clinical trial in patients with a baseline HbA1c ≤8%, the basal insulin dose was decreased by 20% when treatment with MOUNJARO was initiated (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

4.2 Recommended Dose and Dosage Adjustment

- The recommended starting dose of MOUNJARO is 2.5 mg injected subcutaneously only once weekly. The 2.5 mg dosage is for treatment initiation and is not intended for glycemic control. After 4 weeks, increase the dose to 5 mg injected subcutaneously once weekly.
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after no less than 4 weeks on the current dose.
- The maximum dose is 15 mg injected subcutaneously once weekly.
- Renal Insufficiency: No dose adjustment is required in patients with renal impairment (see 10.3 Pharmacokinetics).
- Hepatic Insufficiency: No dose adjustment is recommended in patients with hepatic insufficiency (see 10.3 Pharmacokinetics).
- Geriatrics (≥65 years): No dose adjustment is required in patients over 65 years of age (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics).
- Pediatrics (<18 years): The safety and effectiveness of MOUNJARO have not been studied in patients under 18 years of age. MOUNJARO is not indicated for pediatric use (see 7.1.3 Pediatrics).

4.4 Administration

- Prior to initiation of MOUNJARO, train patients on proper injection technique. Advise the patient to carefully read the Instructions for Use included with the Patient Medication Information leaflet before administering the medicinal product.

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- Patients using the single-dose vial must be instructed to use a syringe equipped with a needle appropriate for subcutaneous injection (for example, a tuberculin or insulin syringe with a 28- to 31-gauge needle more than 2.1 mm in length that is capable of measuring a 0.5 mL dose volume).
- Administer MOUNJARO once weekly, any time of day, with or without meals. MOUNJARO should not be administered daily.
- MOUNJARO is to be injected subcutaneously in the abdomen, in the thigh, or in the upper arm. Rotate injection sites with each dose.
- Visually inspect MOUNJARO before use. It should appear clear and colourless to slightly yellow. Do not use MOUNJARO if particulate matter or discoloration is seen.
- When using MOUNJARO with insulin, administer as separate injections and never mix. It is acceptable to inject MOUNJARO and insulin in the same body region, but the injections should not be adjacent to each other.
- MOUNJARO should not be administered intramuscularly or intravenously.
- Patients using the single-dose prefilled pen or vial go through 4 different pens or vials per month.
- Patients using the multi-dose prefilled pen (MOUNJARO KwikPen) go through 1 MOUNJARO KwikPen per month as one pen delivers 4 doses of the same concentration of tirzepatide.

4.5 Missed Dose

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

Changing Weekly Dosing Schedule

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

5 OVERDOSAGE

Potential symptoms from an overdose could be gastrointestinal related (e.g., nausea). In the event of overdose, appropriate supportive care (including frequent blood glucose monitoring) should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of MOUNJARO.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

MOUNJARO is a clear and colourless to slightly yellow solution that is free of particles. Table 1 lists the dosage forms, strengths, composition, and packaging for each presentation.

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Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Sterile solution of tirzepatide for injection in a single-dose prefilled pen and single-dose vial 2.5 mg/0.5 mL 5 mg/0.5 mL 7.5 mg/0.5 mL 10 mg/0.5 mL 12.5 mg/0.5 mL 15 mg/0.5 mL	Hydrochloric acid solution, sodium chloride, sodium hydroxide solution, sodium phosphate dibasic heptahydrate, water for injection (preservative-free).
Subcutaneous	Sterile solution of tirzepatide for injection in a multi-dose prefilled pen (MOUNJARO KwikPen) 4 doses of 2.5 mg/0.6 mL (10 mg in 2.4 mL) 4 doses of 5 mg/0.6 mL (20 mg in 2.4 mL) 4 doses of 7.5 mg/0.6 mL (30 mg in 2.4 mL) 4 doses of 10 mg/0.6 mL (40 mg in 2.4 mL) 4 doses of 12.5 mg/0.6 mL (50 mg in 2.4 mL) 4 doses of 15 mg/0.6 mL (60 mg in 2.4 mL)	Benzyl alcohol (preservative), glycerin, hydrochloric acid solution, phenol (preservative), sodium chloride, sodium hydroxide solution, sodium phosphate dibasic heptahydrate, water for injection.

MOUNJARO is packaged in a cardboard outer carton and is available in packs of 4 single-dose prefilled pens, or individual single-dose vial.

MOUNJARO KwikPen is packaged in a cardboard outer carton and is available as an individual multi-dose prefilled pen.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

MOUNJARO KwikPen contains 5.4 mg benzyl alcohol in each 0.6 mL dose. Patients with hepatic or renal impairment should be informed of the potential risk of metabolic acidosis due to accumulation of benzyl alcohol over time. Benzyl alcohol may cause allergic reactions (see 2 CONTRAINDICATIONS).

Carcinogenesis and Mutagenesis

Risk of Thyroid C-Cell Tumors

Tirzepatide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) in both sexes of rats in a two-year study at clinically relevant plasma exposures (see 16 NON-CLINICAL TOXICOLOGY). It is unknown whether MOUNJARO causes thyroid C-cell tumors, including MTC, in humans as human relevance could not be determined. Thyroid C-cell tumors in rodents are a known effect for GLP-1 receptor agonists.

MOUNJARO 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 for MTC with the use of MOUNJARO and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

In registration clinical trials, there were no cases of MTC observed in patients treated with MOUNJARO.

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It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity of serum calcitonin and a high background incidence of thyroid disease. However, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. Similarly, patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation.

Cardiovascular

Heart Rate Increase

MOUNJARO causes an increase in heart rate. Caution should be observed in patients who have cardiac conditions that might be worsened by an increase in heart rate (see 9.4).

Heart Failure

There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV.

Endocrine and Metabolism

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients receiving MOUNJARO in combination with an insulin secretagogue (e.g., a sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of the insulin secretagogue or insulin (see 8.2 Clinical Trial Adverse Reactions, 9.2 Drug Interactions Overview).

Other Incretin Drugs

The use of MOUNJARO in combination with other incretin drugs (e.g., GLP-1 receptor agonists or DPP-4 inhibitors) has not been studied and MOUNJARO should not be used in combination with those drugs. It is unknown if concomitant use of drugs acting via similar pathways affects the efficacy and safety of MOUNJARO.

Gastrointestinal

Use of MOUNJARO has been associated with gastrointestinal adverse reactions, sometimes severe (see 8.2 Clinical Trial Adverse Reactions). MOUNJARO has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and therefore should be used with caution in these patients. Events related to impaired gastric emptying, including severe gastroparesis, have been reported. Monitor and consider dose modification or discontinuation in patients who develop severe gastrointestinal symptoms while on treatment.

Malnutrition

Malnutrition has been reported in patients receiving MOUNJARO, including severe, serious and fatal events. Nutritional guidance and supplementation should be considered for patients receiving MOUNJARO. Discontinuation should be considered for severe or persistent cases of malnutrition.

Hepatic/Biliary

Acute Gallbladder Disease

Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist clinical trials and post-marketing.

In MOUNJARO placebo-controlled trials, acute gallbladder disease (i.e., acute cholecystitis, biliary colic, and cholecystectomy) was reported by 0.6% of MOUNJARO-treated patients and 0% of placebo-treated patients.

If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

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Immune

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with MOUNJARO in clinical trials. There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylactic reactions and angioedema) in patients treated with MOUNJARO. If hypersensitivity reactions occur, discontinue use of MOUNJARO; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to tirzepatide or any of the excipients in MOUNJARO (see 2 CONTRAINDICATIONS).

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

Monitoring and Laboratory Tests

Regular self-monitoring of blood glucose is not needed in order to adjust the dose of MOUNJARO. However, when initiating treatment with MOUNJARO in combination with a sulfonylurea or insulin, self-monitoring of blood glucose may become necessary to reduce the dose of the sulfonylurea or insulin in order to reduce the risk of hypoglycemia.

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurement of HbA1c levels, with a goal of decreasing these levels towards the normal range. HbA1c is useful for evaluating long-term glycemic control.

Ophthalmologic

Diabetic Retinopathy Complications

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. MOUNJARO has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema, and should be used with caution in these patients, with appropriate monitoring.

Pancreatic

Pancreatitis

Acute pancreatitis has been observed in patients treated with GLP-1 receptor agonists. In MOUNJARO clinical studies, 14 events of acute pancreatitis were confirmed by adjudication in 13 (0.2%) MOUNJARO-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 (0.1%) comparator-treated patients (0.11 patients per 100 years of exposure).

After initiation of MOUNJARO, observe patients carefully for signs and symptoms of pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. In the absence of other signs and symptoms of pancreatitis, elevations in pancreatic enzymes alone are not predictive of pancreatitis. If pancreatitis is suspected, MOUNJARO should be discontinued and appropriate management initiated; if confirmed, MOUNJARO should not be restarted. MOUNJARO has not been evaluated in patients with a prior history of pancreatitis and should be used with caution in these patients.

Peri-operative considerations

Aspiration during General Anesthesia or Deep Sedation

MOUNJARO delays gastric emptying. Pulmonary aspiration has been reported in patients receiving long-acting GLP-1 receptor agonists undergoing general anesthesia or deep sedation. For the safe management of patients, consider the benefits and risks, and advise patients of these, prior to such procedures.

Psychiatric

Suicidal Ideation and Behaviour

Monitor patients treated with MOUNJARO for the emergence or worsening of depression, suicidal thoughts or behaviours, and/or any unusual changes in mood or behaviour. Consider the benefits and risks to individual

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patients prior to initiating or continuing therapy in patients with suicidal thoughts or behaviours, or those who have a history of suicidal attempts.

Renal

Acute Kidney Injury

MOUNJARO has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhea (see 8 ADVERSE REACTIONS). These events may lead to dehydration, which could cause a deterioration in renal function including acute renal failure.

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 MOUNJARO in patients reporting severe adverse gastrointestinal reactions.

Reproductive Health: Female and Male Potential

Women of childbearing potential are recommended to use contraception when treated with tirzepatide. MOUNJARO is contraindicated during pregnancy (see 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women, and 16 NON-CLINICAL TOXICOLOGY).

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 MOUNJARO (see 9.4 Drug-Drug Interactions).

7.1 Special Populations

7.1.1 Pregnant Women

No clinical trials in pregnant women have been conducted. Studies in animals (i.e., rats and rabbits) have shown reproductive and developmental toxicity, including harm to fetal development and maternal weight loss (see 16 NON-CLINICAL TOXICOLOGY). The extent of exposure in pregnancy during clinical trials is very limited and has been reported in individual cases only.

MOUNJARO is contraindicated during pregnancy (see 2 CONTRAINDICATIONS). If a patient wishes to become pregnant, MOUNJARO should be discontinued at least 1 month before a planned pregnancy due to the long half-life of MOUNJARO.

7.1.2 Breast-feeding

There are no data on the presence of tirzepatide in human milk, the effects on the breastfed infant, or the effects on milk production. MOUNJARO is contraindicated for the duration of breast-feeding (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Safety and effectiveness of MOUNJARO have not been established in pediatric patients. MOUNJARO is not indicated for use in patients younger than 18 years.

7.1.4 Geriatrics

No dose adjustment is required in patients over 65 years of age (see 10.3 Pharmacokinetics).

In clinical trials,1539 (30.1%) MOUNJARO-treated patients were 65 years of age or older and 212 (4.1%) MOUNJARO-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.

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7.1.5 Hepatic Impairment

In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no change in tirzepatide pharmacokinetics (PK) was observed (see 10.3 Pharmacokinetics). However, there is limited clinical experience in patients with mild, moderate, or severe hepatic impairment; therefore, use MOUNJARO with caution in these patient populations.

7.1.6 Renal Impairment

In clinical trials, 2140 (39.5%) of MOUNJARO-treated patients had mild renal impairment (eGFR ≥60 but <90 mL/min/1.73 m^2), 393 (7.3%) MOUNJARO-treated patients had moderate renal impairment (eGFR ≥30 but <60 mL/min/1.73 m^2) and 12 (0.2%) had severe renal impairment (eGFR <30 mL/min/1.73 m^2) at baseline. MOUNJARO is not recommended in patients with end stage renal impairment due to very limited clinical experience with MOUNJARO in this population (see 10.3 Pharmacokinetics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea, diarrhea and vomiting. In general, these reactions were mild or moderate in severity. Gastrointestinal adverse reactions (4.2%) were the most common reasons for treatment discontinuation (see 8.2 Clinical Trial Adverse Reactions). The following serious adverse reactions are described below or elsewhere in the Product Monograph:

- Risk of Thyroid C-cell Tumors (see 7 WARNINGS AND PRECAUTIONS)
- Pancreatitis (see 7 WARNINGS AND PRECAUTIONS)
- Diabetic Retinopathy Complications (see 7 WARNINGS AND PRECAUTIONS)
- Use with Medications Known to Cause Hypoglycemia (see 7 WARNINGS AND PRECAUTIONS)
- Renal Insufficiency (see 7WARNINGS AND PRECAUTIONS)
- Suicidal Ideation and Behaviour (see 7 WARNINGS AND PRECAUTIONS)
- Aspiration during General Anesthesia or Deep Sedation (see 7WARNINGS AND PRECAUTIONS)
- Malnutrition (see 7 WARNINGS AND PRECAUTIONS)

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

All phase 3 studies assessed MOUNJARO 5 mg, 10 mg and 15 mg.

Pool of Placebo-Controlled Trials

The placebo-controlled data in Table 2 are derived from 2 trials (1 monotherapy trial and 1 trial in combination with basal insulin with or without metformin) in patients with type 2 diabetes mellitus (see 14). These data reflect exposure of 718 patients to MOUNJARO and a mean duration of exposure to MOUNJARO of 36.6 weeks.

Pool of Phase 3 Placebo and Active-Controlled Trials

The MOUNJARO data for all phase 3 trials in Table 2 are derived from a pool of patients with type 2 diabetes mellitus participating in 7 placebo- or active-controlled Phase 3 glycemic control trials (see 14) evaluating the use of MOUNJARO as monotherapy and add-on therapy to oral glucose-lowering medications or insulin. In

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this pool, a total of 5119 patients with type 2 diabetes mellitus were treated with MOUNJARO for a mean duration of 48.1 weeks.

Common Adverse Reactions

Table 2 shows common adverse reactions, excluding hypoglycemia (shown in Table 3), associated with the use of MOUNJARO in the pool of placebo-controlled and pool of phase 3 placebo- and active-controlled trials. These adverse reactions occurred more commonly with MOUNJARO than with placebo, and occurred in at least 1% of patients treated with MOUNJARO.

Table 2: Adverse Reactions in Phase 3 Trials Reported in ≥1% of MOUNJARO-Treated Adult Patients with Type 2 Diabetes Mellitus

Adverse Reaction	Placebo-Controlled Trials				All Phase 3 Trials		
	MOUNJARO 5 mg N=237 n (%)	MOUNJARO 10 mg N=240 n (%)	MOUNJARO 15 mg N=241 n (%)	Placebo N=235 n (%)	MOUNJARO 5 mg N=1701 n (%)	MOUNJARO 10 mg N=1702 n (%)	MOUNJARO 15 mg N=1716 n (%)
Gastrointestinal Disorders							
Nausea	29 (12.2)	37 (15.4)	44 (18.3)	10 (4.3)	224 (13.2)	312 (18.3)	381 (22.2)
Diarrhea	28 (11.8)	32 (13.3)	40 (16.6)	21 (8.9)	224 (13.2)	269 (15.8)	275 (16.0)
Vomiting	12 (5.1)	12 (5.0)	22 (9.1)	5 (2.1)	93 (5.5)	132 (7.8)	167 (9.7)
Dyspepsia	19 (8.0)	18 (7.5)	13 (5.4)	6 (2.6)	101 (5.9)	125 (7.3)	115 (6.7)
Constipation	14 (5.9)	14 (5.8)	16 (6.6)	3 (1.3)	111 (6.5)	112 (6.6)	112 (6.5)
Abdominal pain	14 (5.9)	11 (4.6)	13 (5.4)	10 (4.3)	123 (7.2)	137 (8.0)	170 (9.9)
Abdominal distension	1 (0.4)	7 (2.9)	2 (0.8)	1 (0.4)	49 (2.9)	51 (3.0)	58 (3.4)
Eructation	7 (3.0)	6 (2.5)	8 (3.3)	1 (0.4)	36 (2.1)	50 (2.9)	60 (3.5)
Flatulence	3 (1.3)	6 (2.5)	7 (2.9)	0	34 (2.0)	52 (3.1)	46 (2.7)
Gastroesophageal reflux disease	4 (1.7)	6 (2.5)	4 (1.7)	1 (0.4)	27 (1.6)	43 (2.5)	46 (2.7)
General Disorders and Administration Site Conditions							
Fatigue	7 (3.0)	6 (2.5)	10 (4.1)	0	57 (3.3)	66 (3.9)	104 (6.1)
Injection site reaction	7 (3.0)	6 (2.5)	10 (4.1)	1 (0.4)	33 (1.9)	46 (2.7)	60 (3.5)
Investigation							
Weight decreased	0	1 (0.4)	2 (0.8)	0	25 (1.5)	37 (2.2)	42 (2.4)
Heart rate increased	3 (1.3)	1 (0.4)	4 (1.7)	1 (0.4)	5 (0.3)	4 (0.2)	5 (0.3)
Metabolism and Nutrition Disorders							
Decreased appetite	13 (5.5)	23 (9.6)	27 (11.2)	3 (1.3)	132 (7.8)	166 (9.8)	200 (11.7)

Gastrointestinal Adverse Reactions

In the pool of phase 3 placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving MOUNJARO than patients receiving placebo: MOUNJARO 5 mg (37.1%),

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MOUNJARO 10 mg (39.6%), MOUNJARO 15 mg (43.6%), (placebo 20.4%). These events were typically mild or moderate in severity. More patients receiving MOUNJARO 5 mg (3.0%), MOUNJARO 10 mg (5.4%), and MOUNJARO 15 mg (6.6%) discontinued treatment due to gastrointestinal adverse reactions compared to patients receiving placebo (0.4%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation and decreased over time.

In the pool of 7 phase 3 registration studies (placebo-controlled plus active comparator), gastrointestinal events occurred in 38.0% of patients on MOUNJARO 5 mg, 43.8% of patients on MOUNJARO 10 mg, and 48.8% of patients on MOUNJARO 15 mg. For patients who reported gastrointestinal adverse reactions, investigators graded the maximum severity of gastrointestinal adverse reactions occurring on MOUNJARO 5 mg, 10 mg, and 15 mg as "mild" in 66%, 66%, and 65% of patients, “moderate” in 29%, 30%, 32%, or "severe" in 5%, 4%, and 3% of patients, respectively.

Other Adverse Reactions

Hypoglycemia

Table 3 summarizes the incidence of hypoglycemic events in the placebo-controlled trials.

Table 3: Hypoglycemia Adverse Reactions in Placebo-Controlled Trials in Patients with Type 2 Diabetes Mellitus

	MOUNJARO 5 mg n (%)	MOUNJARO 10 mg n (%)	MOUNJARO 15 mg n (%)	Placebo n (%)
Monotherapy				
(40 weeks)*	N=121	N=119	N=120	N=115
Severe hypoglycemia**	0	0	0	0
Severe hypoglycemia or hypoglycemia with glucose level <3 mmol/L	0	0	0	1 (0.9)
Symptomatic hypoglycemia with glucose level ≤3.9 mmol/L	3 (2.5)	8 (6.7)	5 (4.2)	1 (0.9)
Add-on to Basal Insulin with or without Metformin				
(40 weeks)*	N=116	N=119	N=120	N=120
Severe hypoglycemia**	0	2 (1.7)	1 (0.8)	0
Severe hypoglycemia or hypoglycemia with glucose level <3 mmol/L	18 (15.5)	23 (19.3)	17 (14.2)	15 (12.5)
Symptomatic hypoglycemia with glucose level ≤3.9 mmol/L	41 (35.3)	47 (39.5)	45 (37.5)	46 (38.3)

* Data includes events occurring during 4 weeks of treatment-free safety follow-up. Events after the 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 MOUNJARO was used in combination with a sulfonylurea or basal insulin than when used with non-secretagogues (see 7 WARNINGS AND PRECAUTIONS). In study SURPASS-4, severe hypoglycemia occurred in 0.5%, 0.0%, 0.6% and 1.1% of patients when MOUNJARO 5 mg, 10 mg, 15 mg or insulin glargine, respectively, was co-administered with a sulfonylurea. Severe hypoglycemia or hypoglycemia with glucose <3.0 mmol/L occurred in 13.8%, 9.9%, 12.9% and 21.6% of patients when MOUNJARO 5 mg, 10 mg, 15 mg or insulin glargine, respectively, was co-administered with a sulfonylurea.

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In the SURPASS-2 study, severe hypoglycemia or hypoglycemia with glucose <3.0 mmol/L occurred in 0.9%, 0.2%, 1.7% and 0.4% of patients when MOUNJARO 5 mg, 10 mg, 15 mg or semaglutide 1 mg, respectively, was co-administered with metformin.

In the SURPASS-3 study, no cases of severe hypoglycemia occurred when MOUNJARO 5 mg, 10 mg, 15 mg or insulin degludec, was co-administered with a SGLT2i. Severe hypoglycemia or hypoglycemia with glucose <3.0 mmol/L occurred in 1.8%, 1.7%, 2.7% and 8.6% of patients when MOUNJARO 5 mg, 10 mg, 15 mg or insulin degludec, respectively, was co-administered with a SGLT2i.

Immunogenicity

Across seven Phase 3 clinical studies, 2,570 (51.1%) MOUNJARO-treated patients developed anti-drug antibodies (ADAs). Of the 2,570 MOUNJARO-treated patients that developed tirzepatide ADAs, 94 (1.9% of the overall population) and 107 (2.1% of the overall population) had neutralizing antibodies against tirzepatide activity on the GIP and GLP-1 receptors, respectively, and 43 (0.9% of the overall population) and 18 (0.4% of the overall population) had neutralizing antibodies against native GIP and GLP-1, respectively. There was no evidence of an altered pharmacokinetic profile, or an impact on efficacy and safety associated with the development of ADAs.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity (including neutralizing antibody) in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to tirzepatide cannot be directly compared with the incidence of antibodies of other products.

Hypersensitivity Reactions

Hypersensitivity reactions, sometimes severe (e.g., urticaria and eczema), have been reported in clinical trials with MOUNJARO.

In the pool of placebo-controlled trials, hypersensitivity reactions were reported in 3.2% of MOUNJARO-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 MOUNJARO-treated patients with anti-tirzepatide antibodies and in 73/2,455 (3.0%) of MOUNJARO-treated patients who did not develop anti-tirzepatide antibodies (see 7 WARNINGS AND PRECAUTIONS).

Injection Site Reactions

In the pool of placebo-controlled trials, injection site reactions were reported in 3.2% of MOUNJARO-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 MOUNJARO-treated patients with anti-tirzepatide antibodies and in 18/2,455 (0.7%) of MOUNJARO-treated patients who did not develop anti-tirzepatide antibodies.

8.3 Less Common Clinical Trial Adverse Reactions

Hepatobiliary disorders: acute gallbladder disease
Pancreatic disorders: pancreatitis
Nervous System Disorders: dysgeusia

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Pancreatic Enzymes

Amylase and lipase were measured in the clinical trials. Treatment with tirzepatide resulted in mean increases from baseline in pancreatic amylase of 33% to 38% and lipase of 31% to 42%. The percentage of patients with values above 3 times the upper limit of normal for amylase or lipase at any timepoint on-treatment after baseline are presented below. The clinical significance of elevations of amylase or lipase in patients without other signs and symptoms of pancreatitis is unknown (see 7 WARNINGS AND PRECAUTIONS).

Table 4: Amylase and Lipase

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	Placebo-Controlled Trials				All Phase 3 Trials		
	MOUNJARO 5 mg N= 237 n (%)	MOUNJARO 10 mg N= 240 n (%)	MOUNJARO 15 mg N= 241 n (%)	Placebo N= 235 n (%)	MOUNJARO 5 mg N= 1701 n (%)	MOUNJARO 10 mg N= 1702 n (%)	MOUNJARO 15 mg N= 1716 n (%)
Amylase > 3X ULN	5 (2.1)	1 (0.4)	2 (0.8)	0	31 (1.8)	38 (2.2)	30 (1.7)
Lipase > 3X ULN	16 (6.8)	15 (6.3)	13 (5.4)	6 (2.6)	131 (7.7)	146 (8.6)	165 (9.4)

%: percentage of patients; N: number of patients; ULN: upper limit of normal

8.5 Post-market Adverse Reactions

The following additional adverse reactions have been reported during post-approval use of MOUNJARO. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: ileus

Immune system disorders: anaphylactic reaction

Nervous system disorders: dysesthesia

Skin and subcutaneous tissue disorders: angioedema

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

MOUNJARO delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses. Dose adjustments with concomitant use of insulin secretagogues (e.g., sulfonylurea) or insulin may be necessary (see 7 WARNINGS AND PRECAUTIONS and 8.2 Clinical Trial Adverse Reactions).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5: Established or Potential Drug-Drug Interactions

Proper/Common Name	Source of Evidence	Effect	Clinical Comment
Acetaminophen	Clinical Trial	Following the first dose of tirzepatide 5 mg, acetaminophen C_{max} was reduced by 50%, and the median t_{max} occurred 1 hour later. After co-administration for 4 weeks, there was no meaningful impact on acetaminophen C_{max} and t_{max}. Overall acetaminophen exposure (AUC_{0-24hr}) was not influenced.	No dose adjustment of acetaminophen is necessary when administered with tirzepatide.

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Oral Contraceptives	Clinical Trial	Administration of a combination oral contraceptive (0.035 mg ethinyl estradiol plus 0.25 mg norgestimate) in the presence of a single dose of tirzepatide (5 mg) resulted in a reduction of oral contraceptive C_{max} by 55 to 66%, with a 16 to 23% reduction in AUC and a delay in t_{max} of 2.5 to 4.5 hours. These effects may be due to the impact of MOUNJARO on gastric emptying.	Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or to add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO.
Drugs that Increase Heart Rate	Clinical Trial	MOUNJARO resulted in a mean increase in heart rate of 2 to 4 beats per minute. There was a mean increase in heart rate of 0.7 beats per minute in placebo-treated patients.	Caution should be observed if MOUNJARO is administered with other drugs that also increase heart rate, such as drugs with sympathomimetic or anticholinergic activity (see 7 WARNINGS AND PRECAUTIONS).

Drugs that Cause PR Interval or QTc Interval Prolongation

In phase 3 clinical studies, no clinically meaningful treatment-emergent differences in PR interval or QTc duration were noted between placebo, tirzepatide, or comparators.

A dedicated thorough QT study has not been conducted with MOUNJARO.

9.5 Drug-Food Interactions

Interactions with food have not been studied.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

9.8 Drug-Lifestyle Interactions

No studies on the effects of the ability to drive and use machines have been performed. When MOUNJARO is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycemia while driving and using machines.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tirzepatide is a GIP and a GLP-1 receptor agonist. It is an amino acid sequence with a C20-fatty diacid moiety that enables albumin binding and prolongs the half-life.

Tirzepatide is selective to human GIP and GLP-1 receptors. The activity of tirzepatide on the GIP receptor is similar to native GIP hormone. The activity of tirzepatide on the GLP-1 receptor is lower compared to native GLP-1 hormone.

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Tirzepatide enhances first- and second-phase insulin secretion, and reduces plasma glucagon levels, both in a glucose-dependent manner.

10.2 Pharmacodynamics

Tirzepatide lowers fasting and postprandial glucose concentrations through the mechanisms described below, and is associated with reduced food intake, in patients with type 2 diabetes.

Insulin Secretion

In a hyperglycemic clamp study in patients with type 2 diabetes mellitus, tirzepatide 15 mg enhanced the first- and second-phase insulin secretion rate (Figure 1).

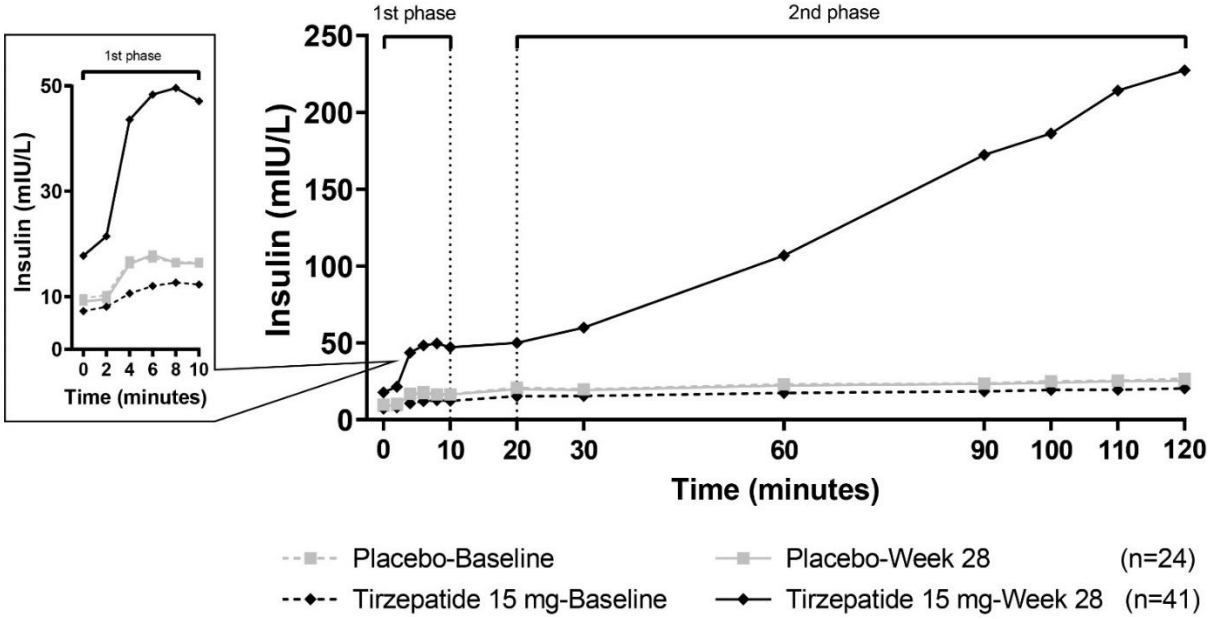

Figure 1: Mean Insulin Concentration at 0-120 Minutes During Hyperglycemic Clamp at Baseline and Week 28

Insulin Sensitivity

In a hyperinsulinemic euglycemic clamp study, tirzepatide 15 mg increased whole-body insulin sensitivity by 63%, as measured by M-value at 28 weeks. The M-value was unchanged for patients receiving placebo. In this study, tirzepatide also lowered body weight in patients with type 2 diabetes.

Glucagon Concentration

Tirzepatide reduces the fasting and postprandial glucagon concentrations. After 28 weeks of treatment, tirzepatide 15 mg reduced fasting glucagon concentration by 28% and glucagon AUC after a mixed meal by 43%, compared with no change for placebo.

Gastric Emptying

Tirzepatide delays gastric emptying. The delay in gastric emptying with tirzepatide is largest after the first dose and diminishes with subsequent doses.

<u>Vital Signs</u>

Blood Pressure

In placebo-controlled Phase 3 trials, treatment with MOUNJARO resulted in a mean decrease in systolic and diastolic blood pressure of 6 to 9 mmHg and 3 to 4 mmHg, respectively. There was a mean decrease in systolic and diastolic blood pressure of 2 mmHg each in placebo-treated patients.

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Cardiac Electrophysiology

In phase 3 clinical studies, no clinically meaningful treatment-emergent differences in PR interval or QTc duration were noted between placebo, MOUNJARO, or comparators. A dedicated thorough QT study has not been conducted with MOUNJARO.

QTc and PR interval were evaluated using a population pharmacokinetic model-based analyses utilizing all data from healthy participants and patients with T2DM who were given either placebo or tirzepatide in one phase 1 study and two phase 2 studies. Concentration-QTc analysis and concentration-PR interval analysis based upon these three studies did not suggest an association between tirzepatide and QTc prolongation or PR interval duration.

10.3 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 was 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 is approximately 10.3 L. Tirzepatide is highly bound to plasma albumin (99%).

Metabolism

Tirzepatide is metabolized by proteolytic cleavage of the peptide backbone, beta-oxidation of the C20-fatty diacid moiety and amide hydrolysis.

Elimination

The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces. 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.

Special Populations and Conditions

- **Pediatrics:** tirzepatide has not been studied in pediatric patients.
- **Geriatrics:** age had no effect on the pharmacokinetics of tirzepatide.
- **Sex:** sex had no effect on the pharmacokinetics of tirzepatide.
- **Pregnancy and Breast-feeding:** studies characterizing the pharmacokinetics of tirzepatide in pregnant and breast-feeding patients have not been performed.
- **Ethnic Origin:** race had no clinically meaningful effect on the pharmacokinetics of tirzepatide.
- **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 participants with normal hepatic function (see 4 DOSAGE AND ADMINISTRATION and 7.1 Special Populations).
- **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 participants with normal renal function.

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This was also shown for patients with both T2DM and mild, moderate or severe renal insufficiency based on data from clinical studies (see 4 DOSAGE AND ADMINISTRATION and 7.1 Special Populations).

- **Obesity:** pharmacokinetic analyses have demonstrated an observed inverse relationship between body weight and tirzepatide exposure, although there was no clinically relevant impact of weight on glycemic control.

11 STORAGE, STABILITY AND DISPOSAL

MOUNJARO single-dose prefilled pen and vial:

- Store MOUNJARO in a refrigerator at 2°C to 8°C, up to the expiration date. Do not use MOUNJARO beyond the expiration date.
- Do not freeze MOUNJARO. Do not use MOUNJARO if frozen.
- Store MOUNJARO in the original carton to protect from light.
- If needed, each single-dose pen or vial can be stored unrefrigerated for up to 21 days at temperatures not to exceed 30°C.
- The single-dose prefilled pen must be discarded after use in a puncture-resistant container.
- Throw away all opened vials after use, even if there is medicine left in the vial.

MOUNJARO KwikPen multi-dose prefilled pen:

- Store MOUNJARO KwikPen in a refrigerator at 2°C to 8°C up to the expiration date. Do not use MOUNJARO KwikPen beyond the expiration date.
- Do not freeze MOUNJARO KwikPen. Do not use MOUNJARO KwikPen if frozen.
- Protect MOUNJARO KwikPen from light.
- If needed, each multi-dose prefilled KwikPen can be stored unrefrigerated at temperatures not to exceed 30°C for up to 30 days.
- The MOUNJARO KwikPen must be discarded after four weekly doses in a puncture-resistant container or in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Each single-dose prefilled pen or vial delivers one single dose of tirzepatide only.

Each multi-dose prefilled pen (MOUNJARO KwikPen) delivers four doses of tirzepatide.

MOUNJARO should not be used if the pen, KwikPen, or vial is damaged.

MOUNJARO should not be used if it does not appear clear, free of particles, and colourless to slightly yellow.

If the pen, KwikPen or vial is dropped on a hard surface, it should not be used.

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PART II: SCIENTIFIC INFORMATION

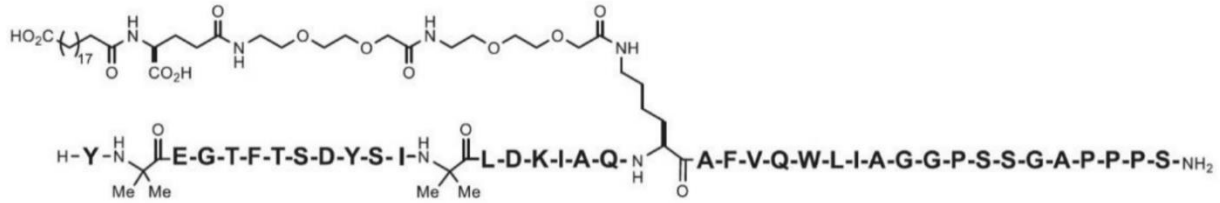
13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper/common name: tirzepatide

Molecular formula and molecular mass: $C_{225}H_{348}N_{48}O_{68}$ and 4813 Dalton

Structural formula:



Physiochemical properties: White to practically white amorphous solid

Table 6: Tirzepatide Substance Solubility Profile

Solvent	Solubility of Tirzepatide (mg/mL)	Part of Solvent Required for 1 Part of Solute (g of Solute per Volume of Solvent)	Solubility Description[a]
5-mM Phosphate Buffer pH 7.0	Not less than 120 at 25°C	8.33 mL to dissolve 1 g	Freely Soluble

[a] Solubility descriptions are consistent with the USP, Ph.Eur., and Japanese Pharmacopoeias

Product Characteristics:

MOUNJARO (tirzepatide injection), for subcutaneous use, contains tirzepatide, a long-acting once-weekly GIP and GLP-1 receptor agonist. Tirzepatide is based on the GIP sequence and contains aminoisobutyric acid (Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 is attached to 1,20-eicosanedioic acid via a linker. MOUNJARO has a pH of 6.5-7.5.

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14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Glycemic Control in Adult Patients with Type 2 Diabetes

Table 7: Summary of Patient Demographics for Clinical Trials in Type 2 Diabetes

Study #	Study Design	Dosage, Route of Administration and Duration	Background Therapy	Study participants (n=number)	Mean age (Range)	Sex (%)
SURPASS-1	Phase 3, multicenter, randomized, parallel-arm, placebo-controlled, double-blind trial	MOUNJARO: 5 mg, 10 mg, 15 mg, SC, weekly Placebo: SC, weekly Duration: 40 weeks	None	478	54 years (18-88)	52% male 48% female
SURPASS-2	Phase 3, multicenter, randomized, parallel-arm, open label, active comparator-controlled, trial	MOUNJARO: 5 mg, 10 mg, 15 mg, SC, weekly Semaglutide: 1 mg SC, weekly Duration: 40 weeks	Metformin (100%)	1879	57 years (21-91)	47% male 53% female
SURPASS-3	Phase 3, multicenter, randomized, parallel-arm, open label, active comparator-controlled trial	MOUNJARO: 5 mg, 10 mg, 15 mg, SC, weekly Titrated insulin degludec 100 U/mL Duration: 52 weeks	Metformin (100%) SGLT-2i (32%)	1444	57 years (22-84)	56% male 44% female

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SURPASS-4	Phase 3, multicenter, randomized, parallel-arm, open label, active comparator-controlled trial	MOUNJARO: 5 mg, 10 mg, 15 mg, SC, weekly Titrated insulin glargine 100 U/mL Duration: up to 104 weeks (primary outcome 52 weeks)	1-3 background OAMs: +/- Metformin (95%) +/- Sulfonylurea (54%) +/- SGLT-2i (25%)	2002	64 years (32-91)	63% male 37% female
SURPASS-5	Phase 3, multicenter, randomized, parallel-arm, placebo-controlled, double-blind trial	MOUNJARO: 5 mg, 10 mg, 15 mg, SC, weekly Placebo: SC, weekly Duration: 40 weeks	Metformin (83%) Titrated insulin glargine 100 U/mL (100%)	475	61 years (27-83)	56% male 44% female

A total of 6263 patients with type 2 diabetes mellitus and inadequate glycemic control were randomized, of whom 4199 received at least one dose of study drug, in 5 placebo- and/or active-controlled, glycemic control global phase 3 studies to evaluate the safety and efficacy of MOUNJARO. Of these, 2082 (33%) patients were ≥65 years and 317 (5%) were ≥75 years. Patients had an overall mean age of 59 years (range 18 to 91 years). 55% were male and 45% were female. The racial distribution of patients in these studies was 81% White, 7% Asian, 4% African American, and 8% other racial origin. The mean body mass index (BMI) overall was 33 kg/m^2 at baseline, and the duration of diabetes was 9.6 years.

Monotherapy Use of MOUNJARO in Patients with Type 2 Diabetes Mellitus (SURPASS-1)

SURPASS-1 was a 40-week double-blind trial that randomized 478 patients with type 2 diabetes mellitus with inadequate glycemic control with diet and exercise to MOUNJARO 5 mg, 10 mg, or 15 mg once weekly or placebo.

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, 5% were Black or African American, and 35% were Asian; 43% identified as Hispanic or Latino ethnicity.

Monotherapy with MOUNJARO 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 8).

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Table 8: Results at Week 40 in a Trial of MOUNJARO as Monotherapy in Adult Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control with Diet and Exercise

	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg	Placebo
Modified Intent-to-Treat (mITT) Population (N)[a]	121	121	120	113
Primary Endpoint				
HbA1c (%)				
Baseline (mean)	8.0	7.9	7.9	8.1
Change at Week 40[b]	-1.8	-1.7	-1.7	-0.1
Difference from placebo[b] (95% CI)	-1.7 (-2.0, -1.4)	-1.6 (-1.9, -1.3)	-1.6 (-1.9, -1.3)	--
p-value[c]	<0.001	<0.001	<0.001	--
Key Secondary Endpoints				
Patients (%) achieving HbA1c <7%	82[c]	85[c]	78[c]	23
Patients (%) achieving HbA1c <5.7%	31[c]	27[c]	38[c]	1
Fasting Serum Glucose (mmol/L)				
Baseline (mean)	8.5	8.5	8.5	8.6
Change at Week 40[b]	-2.2	-2.2	-2.1	0.2
Difference from placebo[b] (95% CI)	-2.4[c] (-3.0, -1.8)	-2.4[c] (-3.1, -1.8)	-2.3[c] (-3.0, -1.7)	--
Body Weight (kg)				
Baseline (mean)	87.0	86.2	85.5	84.5
Change from baseline[b]	-6.3	-7.0	-7.8	-1.0
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 due to inadvertent enrollment were excluded. At Week 40, the HbA1c data were missing for 6%, 7%, 14%, and 12% of patients randomized to MOUNJARO 5 mg, 10 mg, 15 mg, and placebo, respectively. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 2%, 3%, 2%, and 25% of patients randomized to MOUNJARO 5 mg, 10 mg, 15 mg, and placebo, respectively. Missing Week 40 data were imputed using placebo multiple imputation.

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

[c] p<0.001 for superiority vs. placebo, controlled for multiplicity.

Combination Therapy Use of MOUNJARO in Patients with Type 2 Diabetes Mellitus

Combination with metformin (SURPASS-2)

SURPASS-2 was a 40-week open-label trial (double-blind with respect to MOUNJARO dose assignment) that randomized 1879 patients with type 2 diabetes mellitus with inadequate glycemic control on stable doses of metformin alone to once weekly MOUNJARO 5 mg, 10 mg, or 15 mg or subcutaneous semaglutide 1 mg, all in combination with metformin.

Patients had a mean age of 57 years and 47% were men. The mean duration of type 2 diabetes mellitus was 8.6 years and the mean BMI was 34 kg/m^2. Overall, 83% were White, 4% were Black or African American, and 1% were Asian; 70% identified as Hispanic or Latino ethnicity.

Treatment with MOUNJARO 10 mg and 15 mg once weekly for 40 weeks resulted in a statistically significant reduction in HbA1c compared with semaglutide 1 mg once weekly (see Table 9 and Figure 2).

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Table 9: Results at Week 40 in a Trial of MOUNJARO versus Semaglutide 1 mg in Adult Patients with Type 2 Diabetes Mellitus in Combination with Metformin

	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg	Semaglutide 1 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	470	469	469	468
Primary Endpoint				
HbA1c (%)				
Baseline (mean)	8.3	8.3	8.3	8.3
Change at Week 40[b]	-2.0	-2.2	-2.3	-1.9
Difference from semaglutide[b] (95% CI)	-0.2 (-0.3, -0.0)	-0.4 (-0.5, -0.3)	-0.5 (-0.6, -0.3)	--
p-value	0.018[c]	<0.001[e]	<0.001[e]	--
Key Secondary Endpoints				
Patients (%) achieving HbA1c <7%	82	86[d]	86[d]	79
Patients (%) achieving HbA1c <5.7%	27	40[e]	46[e]	19
Fasting Serum Glucose (mmol/L)				
Baseline (mean)	9.7	9.7	9.6	9.5
Change at Week 40[b]	-3.0	-3.3	-3.3	-2.7
Body Weight (kg)				
Baseline (mean)	92.5	94.8	93.8	93.7
Change from baseline[b]	-7.6	-9.3	-11.2	-5.7
Difference from semaglutide[b] (95% CI)	-1.9[d] (-2.8, -1.0)	-3.6[d] (-4.5, -2.7)	-5.5[d] (-6.4, -4.6)	--

[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 due to inadvertent enrollment were excluded. At Week 40 the HbA1c endpoint was missing for 4%, 5%, 5%, and 5% of patients randomized to MOUNJARO 5 mg, 10 mg, 15 mg, and semaglutide 1 mg, respectively. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 2%, 1%, 1%, and 3% of patients randomized to MOUNJARO 5 mg, 10 mg, 15 mg, and semaglutide 1 mg, respectively. Missing Week 40 data were imputed using multiple imputation with retrieved dropout.

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

[c] $p<0.05$ for superiority vs. semaglutide, controlled for multiplicity.

[d] $p<0.01$ for superiority vs. semaglutide, controlled for multiplicity.

[e] $p<0.001$ for superiority vs. semaglutide, controlled for multiplicity.

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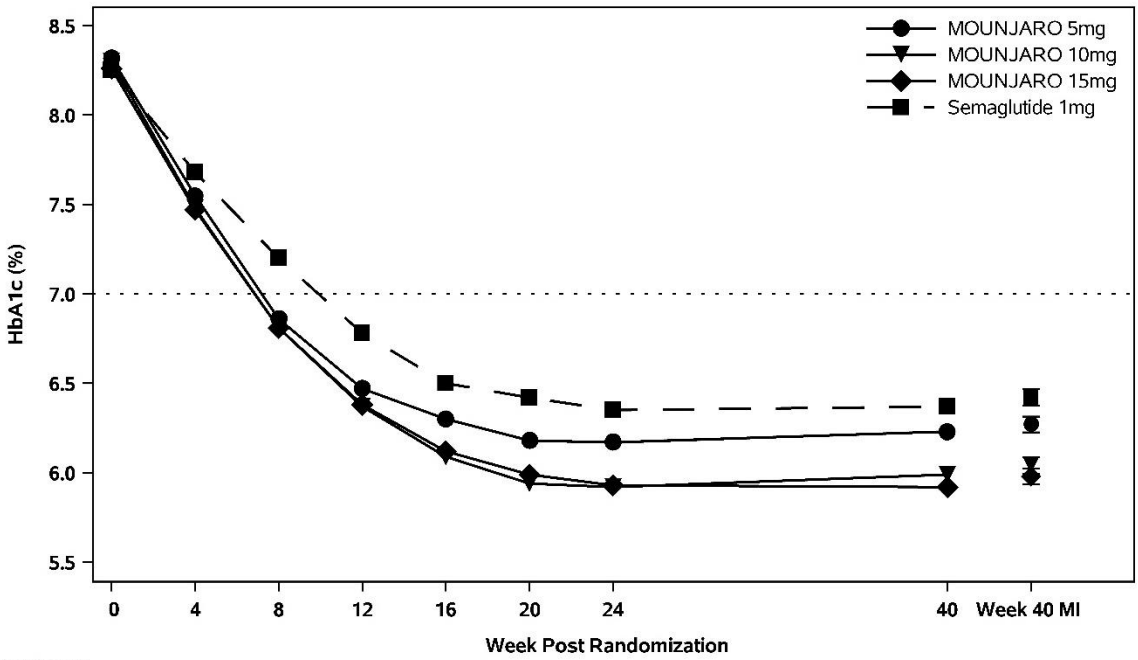

Number of patients			
MOUNJARO 5mg	470	451	470
MOUNJARO 10mg	469	445	469
MOUNJARO 15mg	469	447	469
Semaglutide 1mg	468	443	468

Note: Displayed results are from modified Intent-to-Treat Full Analysis Set. (1) Observed mean value from Week 0 to Week 40, and (2) least squares mean ± standard error at Week 40 multiple imputation (MI).

Figure 2: Mean HbA1c (%) Over Time - Baseline to Week 40

Combination with metformin with or without SGLT-2i (SURPASS-3)

SURPASS-3 was a 52-week open-label trial that randomized 1444 patients with type 2 diabetes mellitus with inadequate glycemic control on stable doses of metformin with or without SGLT2i to once weekly MOUNJARO 5 mg, 10 mg, 15 mg, or titrated insulin degludec 100 units/mL once daily. 32% of patients were on SGLT2i. Patients randomized to insulin degludec initially received 10 units once daily. The dose was adjusted weekly throughout the trial using a treat-to-target algorithm based on self-measured fasting blood glucose values, targeting <5 mmol/L. By the primary endpoint at Week 52, the mean daily insulin degludec dose was 49 U (0.5 U per kilogram) per day.

Patients had a mean age of 57 years and 56% were men. The mean duration of type 2 diabetes mellitus was 8.4 years and the mean BMI was 34 kg/m^2. Overall, 91% were White, 3% were Black or African American, and 5% were Asian; 29% identified as Hispanic or Latino ethnicity.

Treatment with MOUNJARO 10 mg and 15 mg once weekly for 52 weeks resulted in a statistically significant reduction in HbA1c compared with daily insulin degludec (see Table 10 and Figure 3).

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Table 10: Results at Week 52 in a Trial of MOUNJARO versus Insulin Degludec in Adult Patients with Type 2 Diabetes Mellitus in Combination with Metformin with or without SGLT-2i

	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg	Insulin Degludec
Modified Intent-to-Treat (mITT)[a] Population (N)	358	360	358	359
Primary Endpoint				
HbA1c (%)				
Baseline (mean)	8.2	8.2	8.2	8.1
Change at Week 52[b]	-1.9	-2.0	-2.1	-1.3
Difference from insulin degludec[b] (95% CI)	-0.6 (-0.7, -0.5)	-0.8 (-0.9, -0.6)	-0.9 (-1.0, -0.7)	--
p-value[c]	<0.001	<0.001	<0.001	--
Key Secondary Endpoints				
Patients (%) achieving HbA1c <7%	79[c]	82[c]	83[c]	58
Patients (%) achieving HbA1c <5.7%	24	34	41	5
Fasting Serum Glucose (mmol/L)				
Baseline (mean)	9.5	9.5	9.4	9.3
Change at Week 52[b]	-2.6	-2.8	-3.0	-2.8
Body Weight (kg)				
Baseline (mean)	94.4	93.8	94.9	94.0
Change from baseline[b]	-7.0	-9.6	-11.3	1.9
Difference from insulin degludec[b] (95% CI)	-8.9[c] (-10.0, -7.8)	-11.5[c] (-12.6, -10.4)	-13.2[c] (-14.3, -12.1)	--

[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 due to inadvertent enrollment were excluded. At Week 52 the HbA1c endpoint was missing for 6%, 10%, 5%, and 9% of patients randomized to MOUNJARO 5 mg, 10 mg, 15 mg, and insulin degludec, respectively. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 1%, 1%, 2%, and 1% of patients randomized to MOUNJARO 5 mg, 10 mg, 15 mg, and insulin degludec, respectively. Missing Week 52 data were imputed using multiple imputation with retrieved dropout.

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

[c] p<0.001 for superiority vs. insulin degludec, controlled for multiplicity.

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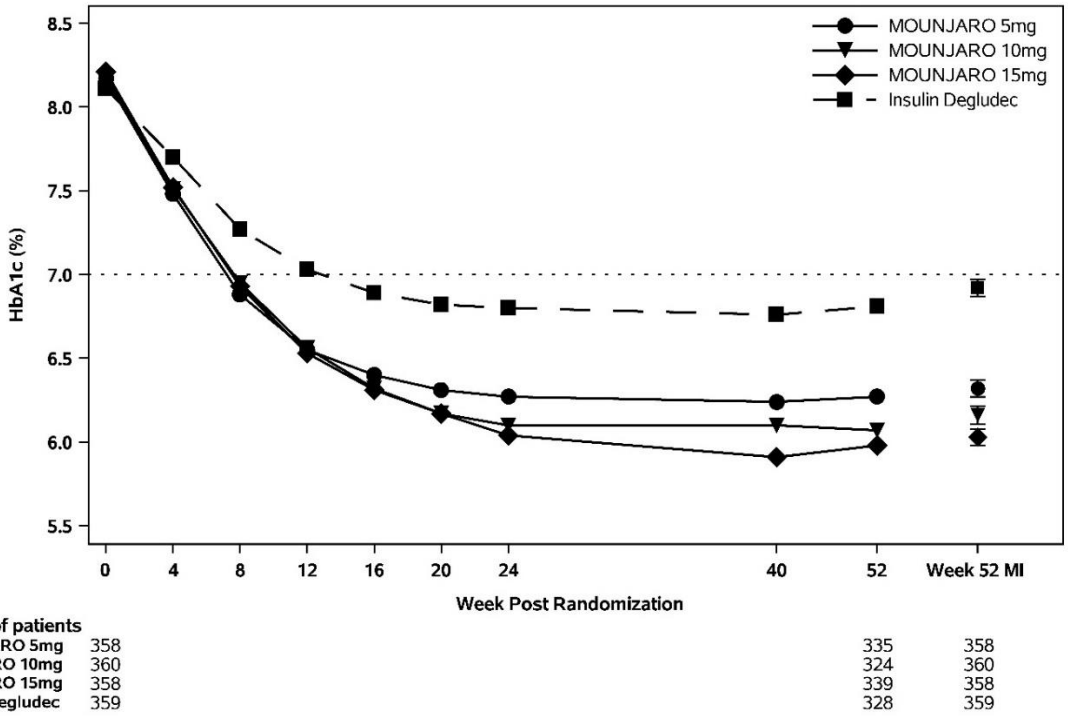

Note: Displayed results are from modified Intent-to-Treat Full Analysis Set. (1) Observed mean value from Week 0 to Week 52, and (2) least squares mean ± standard error at Week 52 multiple imputation (MI).

Figure 3: Mean HbA1c (%) over time - Baseline to Week 52

Combination with metformin, sulfonylurea and/or SGLT-2i (SURPASS-4)

SURPASS-4 was a 104-week open-label trial (52-week primary endpoint) that randomized 2002 patients with type 2 diabetes mellitus with increased cardiovascular risk to MOUNJARO 5 mg, 10 mg, 15 mg once weekly, or insulin glargine 100 units/mL once daily (1:1:1:3 ratio) on a background of metformin (95%) and/or sulfonylureas (54%) and/or SGLT2i (25%) (see Table 11 for further information regarding the number of patients on each combination).

Table 11: Summary of Baseline Antihyperglycemic Medications in SURPASS-4

Background Therapy	MOUNJARO 5 mg (N=329)	MOUNJARO 10 mg (N=328)	MOUNJARO 15 mg (N=338)	Insulin Glargine (N=1000)	Total (N=1995)
Metformin alone	99 (30.1)	107 (32.6)	112 (33.1)	321 (32.1)	639 (32.0)
Metformin plus Sulfonylurea	136 (41.3)	132 (40.2)	124 (36.7)	388 (38.8)	780 (39.1)
Metformin plus SGLT2i	37 (11.2)	37 (11.3)	45 (13.3)	138 (13.8)	257 (12.9)
Metformin plus Sulfonylurea plus SGLT2i	34 (10.3)	40 (12.2)	36 (10.7)	107 (10.7)	217 (10.9)
SU alone	16 (4.9)	8 (2.4)	16 (4.7)	34 (3.4)	74 (3.7)
SGLT2i alone	4 (1.2)	3 (0.9)	2 (0.6)	3 (0.3)	12 (0.6)
SU plus SGLT2i	3 (0.9)	1 (0.3)	3 (0.9)	8 (0.8)	15 (0.8)

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Patients had a mean age of 64 years and 63% were men. The mean duration of type 2 diabetes mellitus was 11.8 years and the mean BMI was 33 kg/m^2. Overall, 82% were White, 4% were Black or African American, and 4% were Asian; 48% identified as Hispanic or Latino ethnicity. Across all treatment groups, 87% of patients had a history of cardiovascular disease as a preexisting condition. At baseline, eGFR was ≥90 mL/min/1.73 m^2 in 43%, 60 to 90 mL/min/1.73 m^2 in 40%, 45 to 60 mL/min/1.73 m^2 in 10%, and 30 to 45 mL/min/1.73 m^2 in 6% of patients.

Patients assigned to insulin glargine were started on a dose of 10 U once daily. The dose was adjusted weekly throughout the trial using a treat-to-target algorithm based on self-measured fasting blood glucose values, targeting <5.6 mmol/L. By the primary endpoint at week 52, the mean daily insulin glargine dose was 44 U (0.5 U per kilogram) per day.

Treatment with MOUNJARO 10 mg and 15 mg once weekly for 52 weeks resulted in a statistically significant reduction in HbA1c compared with insulin glargine once daily (see Table 12 and Figure 4).

Table 12: Results at Week 52 in a Trial of MOUNJARO versus Insulin Glargine in Adult Patients with Type 2 Diabetes Mellitus in Combination with Metformin and/or Sulfonylurea and/or SGLT-2i

	MOUNJARO 5 mg	**MOUNJARO 10 mg**	**MOUNJARO 15 mg**	**Insulin Glargine**
Modified Intent-to-Treat (mITT) Population (N)[a]	328	326	337	998
Primary Endpoint				
HbA1c (%)				
Baseline (mean)	8.5	8.6	8.5	8.5
Change at Week 52[b]	-2.1	-2.3	-2.4	-1.4
Difference from insulin glargine[b] (95% CI)	-0.7 (-0.9, -0.6)	-0.9 (-1.1, -0.8)	-1.0 (-1.2, -0.9)	--
p-value	<0.001	<0.001	<0.001	--
Key Secondary Endpoints				
Patients (%) achieving HbA1c <7%	75[c]	83[c]	85[c]	49
Patients (%) achieving HbA1c <5.7%	22	31	38	4
Fasting Serum Glucose (mmol/L)				
Baseline (mean)	9.6	9.8	9.7	9.4
Change at Week 52[b]	-2.5	-2.8	-3.0	-2.7
Body Weight (kg)				
Baseline (mean)	90.3	90.6	90.0	90.2
Change from baseline[b]	-6.4	-8.9	-10.6	1.7
Difference from insulin glargine[b] (95% CI)	-8.1[c] (-8.9, -7.3)	-10.6[c] (-11.4, -9.8)	-12.2[c] (-13.0, -11.5)	--

[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 due to inadvertent enrollment were excluded. At Week 52 the HbA1c endpoint was missing for 9%, 6%, 4%, and 9% of patients randomized to MOUNJARO 5 mg, 10 mg, 15 mg, and insulin glargine, respectively. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 0%, 0%, 1%, and 1% of patients randomized to MOUNJARO 5 mg, 10 mg, 15 mg, and insulin glargine, respectively. Missing Week 52 data were imputed using multiple imputation with retrieved dropout.

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

[c] p<0.001 for superiority vs. insulin glargine, controlled for multiplicity.

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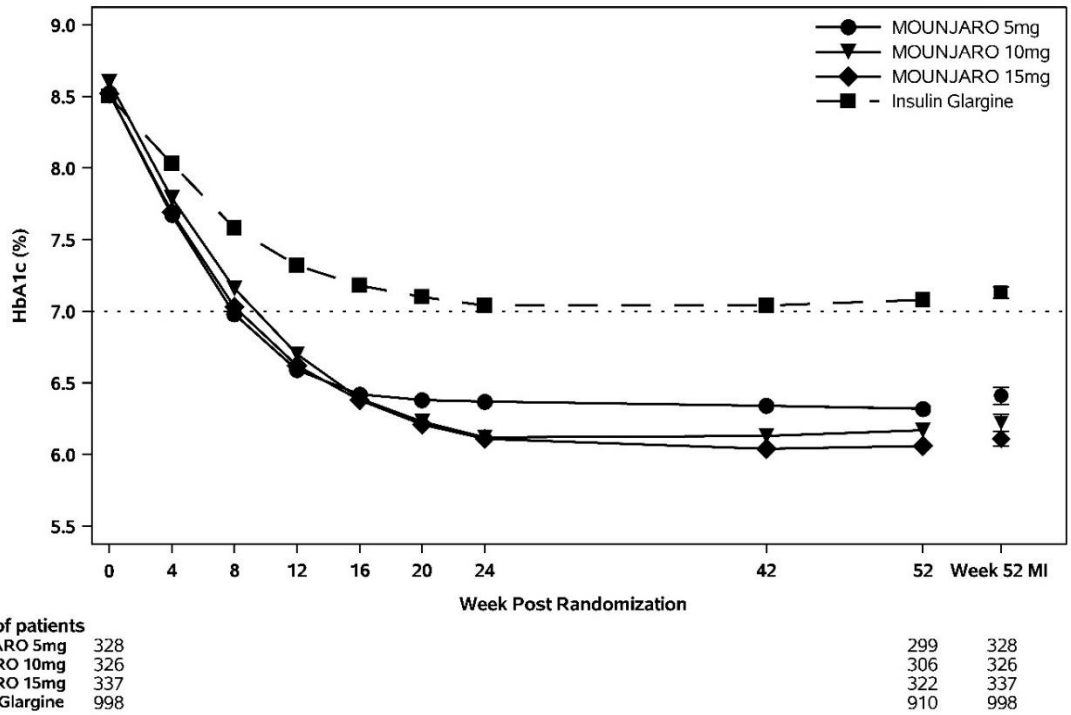

Figure 4: Mean HbA1c (%) Over Time - Baseline to Week 52

Combination with basal insulin with or without metformin (SURPASS-5)

SURPASS-5 was a 40-week double-blind trial that randomized 475 patients with type 2 diabetes mellitus with inadequate glycemic control on insulin glargine 100 units/mL, with or without metformin, to MOUNJARO 5 mg, 10 mg, 15 mg once weekly, or placebo. The dose of background insulin glargine was adjusted using a treat-to-target algorithm based on self-measured fasting blood glucose values, targeting <5.6 mmol/mol.

Patients had a mean age of 61 years and 56% were men. The mean duration of type 2 diabetes mellitus was 13.3 years and the mean BMI was 33 kg/m^2. Overall, 80% were White, 1% were Black or African American, and 18% were Asian; 5% identified as Hispanic or Latino ethnicity.

The mean starting dose of insulin glargine was 34, 32, 35, and 33 units/day for patients receiving MOUNJARO 5 mg, 10 mg, 15 mg, and placebo, respectively. At randomization, the initial insulin glargine dose in patients with HbA1c ≤8.0% was reduced by 20%. At week 40, mean dose of insulin glargine was 38, 36, 29, and 59 units/day for patients receiving MOUNJARO 5 mg, 10 mg, 15 mg, and placebo, respectively.

Treatment with MOUNJARO 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 13).

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Table 13: Results at Week 40 in a Trial of MOUNJARO with Basal Insulin in Adult Patients with Type 2 Diabetes Mellitus with or without Metformin

	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg	Placebo
Modified Intent-to-Treat (mITT) Population (N)[a]	116	118	118	119
Primary Endpoint				
HbA1c (%)				
Baseline (mean)	8.3	8.4	8.2	8.4
Change at Week 40[b]	-2.1	-2.4	-2.3	-0.9
Difference from placebo[b] (95% CI)	-1.2 (-1.5, -1.0)	-1.5 (-1.8, -1.3)	-1.5 (-1.7, -1.2)	--
p-value[c]	<0.001	<0.001	<0.001	--
Key Secondary Endpoints				
Patients (%) achieving HbA1c <7%	87[c]	90[c]	85[c]	35
Patients (%) achieving HbA1c <5.7%	24	42[c]	50[c]	3
Fasting Serum Glucose (mmol/L)				
Baseline (mean)	9.0	9.0	8.9	9.1
Change at Week 40[b]	-3.2	-3.6	-3.5	-2.2
Difference from placebo[b] (95% CI)	-1.1[c] (-1.5, -0.6)	-1.4[c] (-1.8, -1.0)	-1.3[c] (-1.7, -0.9)	--
Body Weight (kg)				
Baseline (mean)	95.8	94.6	96.0	94.2
Change from baseline[b]	-5.4	-7.5	-8.8	1.6
Difference from placebo[b] (95% CI)	-7.1[c] (-8.7, -5.4)	-9.1[c] (-10.7, -7.5)	-10.5[c] (-12.1, -8.8)	--

[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 due to inadvertent enrollment were excluded. At Week 40 the HbA1c endpoint was missing for 6%, 3%, 7%, and 2% of patients randomized to MOUNJARO 5 mg, 10 mg, 15 mg, and placebo, respectively. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 1%, 0%, 1%, and 4% of patients randomized to MOUNJARO 5 mg, 10 mg, 15 mg, and placebo, respectively. Missing Week 40 data were imputed using placebo multiple imputation.

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

[c] p<0.001 for superiority vs. placebo, controlled for multiplicity.

14.2 Comparative Bioavailability Studies

A randomized, multicenter, open-label, two-way, single-dose, crossover comparative bioavailability study of MOUNJARO KwikPen (tirzepatide solution in a multi-dose prefilled pen) and MOUNJARO (tirzepatide injection in a single-dose prefilled pen), administered as 0.6 mL x 5 mg/0.6 mL for MOUNJARO KwikPen and as 0.5 mL x 5 mg/0.5 mL for MOUNJARO subcutaneous injection, was conducted in healthy, adult, female and male participants . Comparative bioavailability data from 62 subjects that were included in the statistical analysis are presented in the following table:

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Table 14: Summary Table of the Comparative Bioavailability Data

Tirzepatide (1 x 5 mg) Geometric Mean (CV%)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T[3] (ng·h/mL)	118000 (22%)	125000 (23%)	94.3	92.6-96.0
AUC_I (ng·h/mL)	119000 (22%)	127000 (22%)	94.8	93.1-96.5
C_{max} (ng/mL)	524 (27%)	649 (31%)	80.8	78.0-83.8
T_{max}[4] (h)	36.0 (8.00-144)	12.0 (7.97-168)		
$T_{1/2}$[5] (h)	126 (81.5-186)	122 (39.0-178)		

1 MOUNJARO® KwikPen® (tirzepatide injection in a multi-dose prefilled pen) Solution, 5 mg/0.6 mL (Eli Lilly Canada Inc.)

2 MOUNJARO® (tirzepatide injection in a single-dose prefilled pen) Solution, 5 mg/0.5 mL (Eli Lilly Canada Inc.)

3 AUC_T= area under the concentration versus time curve from time to t, where t is the last time point with a measurable concentration

4 Expressed as the median (range) only

5 Expressed as the geometric mean (range)

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Tirzepatide was administered twice weekly by subcutaneous injection to rats and cynomolgus monkeys, at doses up to 3 mg/kg (1.96x human exposure based on AUC) and 0.5 mg/kg (1.35x human exposure based on AUC), respectively. Primary findings were consistent with the activity of incretins, including GLP-1R agonists, and included significantly decreased food consumption and body weight loss.

Carcinogenicity: A 2-year carcinogenicity study (lifetime exposure) was conducted with tirzepatide in male and female rats, administered twice weekly by subcutaneous injection, at doses of 0.15, 0.5, and 1.5 mg/kg (0.1-, 0.4-, and 1-fold the maximum recommended human dose (MRHD) of 15 mg once weekly based on AUC). Tirzepatide caused an increase in thyroid C-cell tumors (adenomas and carcinomas combined) in both sexes at all dose levels.

In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered twice weekly by subcutaneous injection was not tumorigenic.

Genotoxicity: Tirzepatide was not genotoxic in a rat bone marrow micronucleus assay at single SC-administered doses up to 3 mg/kg.

Reproductive and Developmental Toxicology: In fertility and early embryonic development studies, male and female rats were administered tirzepatide twice weekly by subcutaneous injection at 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.

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However, 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.

Pregnant rats were given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide (0.03-, 0.1-, 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 reduced fetal weights were observed, in addition to decreases in maternal body weights and food consumption, at 0.5 mg/kg.

Pregnant rabbits were given tirzepatide once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg (0.01-, 0.1-, and 0.23-fold the MRHD) during organogenesis. Adverse effects on the gastrointestinal system resulting in maternal mortality or abortion in a few rabbits were observed at all dose levels. Reduced fetal weights, decreased maternal food consumption and decreased maternal body weights were observed at 0.1 mg/kg.

In a prenatal-postnatal study in F_0 maternal rats administered tirzepatide twice weekly by subcutaneous injection at doses of 0.02, 0.10, or 0.25 mg/kg from implantation through lactation, F_1 pups from F_0 maternal rats given 0.25 mg/kg tirzepatide had lower mean body weight from birth through the end of the study for males and postnatal day 56 for females.

Juvenile Toxicity: Consistent with adult rats, in a juvenile toxicity study in rats, effects were limited to pharmacological effects of tirzepatide on body weight and food consumption and other reversible effects secondary to tirzepatide pharmacology. Tirzepatide led to a delay in sexual maturity in male and female rats, which was attributed to the reduced body weight gain during treatment. These data indicate that tirzepatide does not have specific toxicities in juvenile animals.

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PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrMOUNJARO®
PrMOUNJARO® KwikPen®

tirzepatide injection

The information below applies to MOUNJARO and MOUNJARO KwikPen unless otherwise indicated.

Read this carefully before you start taking MOUNJARO and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about MOUNJARO.

Serious Warnings and Precautions

- Tirzepatide, the medicinal ingredient in MOUNJARO, increased the risk of developing thyroid C-cell tumors in rats. It is not known if the risk seen in rats applies to humans. It is uncertain if MOUNJARO may increase your risk for developing thyroid C-cell tumors, including medullary thyroid carcinoma.
- Do not use MOUNJARO if you:
  - have a personal or family history of Medullary Thyroid Cancer (MTC);
  - have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Your healthcare professional will speak to you about the risk and symptoms of thyroid tumors.

What is MOUNJARO used for?

MOUNJARO is used along with diet and exercise to:

- improve blood sugar levels in adults with type 2 diabetes.

MOUNJARO is used:

- alone, if you cannot take metformin;
- with metformin;
- with metformin and a sulfonylurea;
- with metformin and a sodium-glucose cotransporter 2 inhibitor (SGLT2i);
- with basal insulin (with or without metformin).

How does MOUNJARO work?

MOUNJARO belongs to a class of medicines called GIP and GLP-1 receptor agonists. MOUNJARO lowers your blood sugar by helping your body release more insulin when your blood sugar is high. It also reduces levels of glucagon, a hormone that prevents blood sugar from decreasing too much.

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What are the ingredients in MOUNJARO?

Medicinal ingredients: tirzepatide

Non-medicinal ingredients:

MOUNJARO single-dose pen and single-dose vial (*preservative-free):*

Hydrochloric acid solution, sodium chloride, sodium hydroxide solution, sodium phosphate dibasic heptahydrate, water for injection.

MOUNJARO KwikPen multi-dose pen *(includes preservatives):*

Benzyl alcohol (preservative), glycerin, hydrochloric acid solution, phenol (preservative), sodium chloride, sodium hydroxide solution, sodium phosphate dibasic heptahydrate, water for injection

MOUNJARO comes in the following dosage forms:

MOUNJARO – solution in a single-dose prefilled pen or vial: 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL.

MOUNJARO KwikPen – solution in a multi-dose prefilled pen containing 4 fixed-doses: 2.5 mg/0.6 mL, 5 mg/0.6 mL, 7.5 mg/0.6 mL, 10 mg/0.6 mL, 12.5 mg/0.6 mL, and 15 mg/0.6 mL.

Do not use MOUNJARO if:

- you are allergic to tirzepatide or to any ingredient in MOUNJARO or component of its container. This includes benzyl alcohol, which is used as a preservative in MOUNJARO KwikPen.
- you or a member of your family has ever had Medullary Thyroid Cancer (MTC).
- you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you are pregnant or breast-feeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MOUNJARO. Talk about any health conditions or problems you may have, including if you have:

- type 1 diabetes.
- a heart condition that causes an increase in heart rate.
- experienced severe allergic reactions and swelling when taking GLP-1 receptor agonist medicines.
- ever had diabetic ketoacidosis (increased ketones in the blood or urine).
- severe problems with your stomach (gastroparesis) or food digestion. MOUNJARO slows stomach emptying so food passes more slowly through your stomach.
- very low food intake or inadequate nutrition (including low vitamins and minerals).
- ever had depression or other mental health problems.

Other warnings you should know about:

Gallbladder Disease

- You may suddenly develop symptoms of gallbladder disease when taking MOUNJARO.
- Gallbladder disease can include inflammation of the gallbladder (cholecystitis), or gallstones blocking the bile duct (biliary colic).
- Symptoms may include sudden and intensifying pain in your abdomen, between your shoulder blades or your right shoulder. You should seek immediate medical attention if you experience severe abdominal pain, yellowing of your skin, or high fever with chills. If you think you might have a problem with your gallbladder, consult your healthcare professional.

Benzyl alcohol

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- Benzyl alcohol is a preservative used in MOUNJARO KwikPen. Benzyl alcohol can cause you to develop metabolic acidosis (acid in the blood). Metabolic acidosis can develop when large amounts of benzyl alcohol build-ups in your body. Talk to your healthcare professional if you:
  - are taking other medications containing benzyl alcohol.
  - have liver or kidney problems.

Children and adolescents

- MOUNJARO is not recommended in children and adolescents under 18 years.

Pregnancy and breast-feeding

- Tell your healthcare professional if you are pregnant, planning to become pregnant or think you are pregnant. There are specific risks you should discuss with your healthcare professional.
- You should not take MOUNJARO if you are pregnant. It may harm your unborn baby.
- If you are able to become pregnant:
  - Avoid becoming pregnant while you are taking MOUNJARO. Use effective birth control during treatment and at least one month after your last dose. If you are using oral hormonal drugs as a birth control method:
    - switch to a non-oral hormonal birth control medicine, or
    - add a barrier method of birth control (e.g., condoms). Use this method for 4 weeks when beginning treatment with MOUNJARO and for 4 weeks after each time your dose is increased.
- Do not breastfeed while you are taking MOUNJARO.

Driving and using machines

- Low blood sugar (hypoglycemia) may affect your ability to concentrate. Avoid driving or using machines if you get any signs of low blood sugar.
- See “What are possible side effects from using MOUNJARO” for the warning signs of low blood sugar. Talk to your healthcare professional for further information.

Pancreas problems

- Taking MOUNJARO can cause an inflamed pancreas (acute pancreatitis).
- Speak to your healthcare professional if you have or have had pancreas problems such as inflammation of the pancreas.
- Your healthcare professional will monitor you for any symptoms of acute pancreatitis. Speak to your healthcare professional immediately if you have severe and on-going pain in the stomach area. See “What are possible side effects from using MOUNJARO” for more symptoms of acute pancreatitis.

Serious allergic reactions

- Stop using MOUNJARO and get medical help right away if you have any symptoms of a serious allergic reaction. This can include itching, rash, or difficulty breathing. See “What are possible side effects from using MOUNJARO” for more symptoms of an allergic reaction.

Blood tests

- Your blood sugar levels should be monitored at the start of treatment if you are taking MOUNJARO with anti-diabetic medicines known as sulfonylurea or insulin. Monitoring your blood sugar levels will help reduce the risk of developing hypoglycemia (low blood sugar).

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- Your healthcare professional will monitor your blood sugar levels periodically during your treatment with MOUNJARO.

Kidney problems

- During treatment with MOUNJARO, you may experience feeling sick (nausea) or being sick (vomiting), and diarrhea. These side effects can cause dehydration (loss of fluids). Dehydration can lead to problems with your kidneys, such as sudden kidney failure.
- It is therefore important to drink plenty of fluids to prevent dehydration.
- Talk to your healthcare professional if you have any questions or concerns.

Diabetic eye disease (retinopathy)

- Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disease. This may require treatment or lead to a loss of vision.
- You should inform your healthcare professional if you have diabetic eye disease (retinopathy) or if you experience vision problems during treatment with MOUNJARO.

Gastrointestinal (stomach and intestine) problems

- Stomach problems, sometimes severe, have been reported in people who use MOUNJARO. Tell your healthcare professional if you have stomach problems that are severe or will not go away.

Malnutrition

- Nutrition problems, sometimes severe or serious, have been reported in people who use MOUNJARO. This can cause you to have low vitamin, mineral, and/or protein levels and low body weight.
- While you are using MOUNJARO, your healthcare professional may give you guidance on nutrition and/or recommend you take vitamins or supplements.

Food or liquid getting into lungs during anesthesia

- Some patients taking medicines like MOUNJARO have had problems with food or liquid from their stomach getting into their lungs while under general anesthesia or deep sedation.
- Tell your healthcare professional that you are taking MOUNJARO before you have a procedure that requires general anesthesia or deep sedation.

Depression or thoughts of suicide

- You should pay attention to any changes in your mood, behaviours, feelings, or thoughts. Call your healthcare professional right away if you have any:
  - thoughts or behaviours of harming or killing yourself, or
  - changes to your mental health that are new, worse, or worry you.

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Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MOUNJARO:

- oral birth control medicines.
- anti-diabetic medicines known as a sulfonylurea (e.g., glyburide, gliclazide, glimepiride) or insulin. Combining these medicines with MOUNJARO might increase the risk of getting low blood sugar. Your healthcare professional may tell you to lower your regular dose of these drugs when adding MOUNJARO treatment.
- medicines that may increase your heart rate.
- other incretin medicines. The use of MOUNJARO in combination with other GLP-1 receptor agonists or with DPP-4 inhibitors has not been studied and MOUNJARO should not be used in combination with those drugs.

How to take MOUNJARO:

- Take MOUNJARO exactly as your healthcare professional has prescribed. Do not change your dose or stop taking MOUNJARO without talking to your healthcare professional.
- Set a reminder on a calendar to remind yourself of your weekly dose.
- The pen, KwikPen and vial have glass parts. Handle carefully. If you drop the pen, KwikPen or vial on a hard surface, do not use it. Use a new pen, KwikPen or vial for your injection.
- An Instructions for Use leaflet is enclosed with the MOUNJARO (single-dose prefilled pen, or single-dose vial) and MOUNJARO KwikPen (multi-dose prefilled pen). The Instructions for Use leaflet provides instructions on how to use the prefilled pen, multi-use prefilled pen or vial. Read the Instructions for Use leaflet before you take MOUNJARO or MOUNJARO KwikPen.
- Talk to your healthcare professional about how to correctly administer MOUNJARO before you use it for the first time. If you do not understand the instructions or have any questions, talk with your doctor, diabetes nurse, or pharmacist.
- You can give yourself the injection at any time of the day, with or without food.
- You will be using the following number of pens, vials or KwikPens during a month's treatment:
    - 4 different pens or vials if you are using MOUNJARO single-dose prefilled pen, or single-dose vial.
    - 1 pen if you are using multi-dose prefilled MOUNJARO KwikPen.

How to inject MOUNJARO:

- MOUNJARO is an injection which is given under the skin (subcutaneously). Do not inject MOUNJARO into a vein or muscle.
- The best places to give yourself the injection are your stomach area (abdomen) or upper leg (thigh). Another person should give you the injection in the back of your upper arm.
- Do not use the same site for each injection. Change (rotate) your injection site with each weekly injection.

Your dose of MOUNJARO may change depending on:

- if you are taking other diabetic medication
- your physical health (e.g., weight, illness, physical activity)
- your diet

Changing the day of your weekly injection:

- If necessary, you can change the day of your weekly injection. There has to be at least 3 days since your last injection of MOUNJARO.

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If you give yourself insulin in addition to MOUNJARO:

- Never mix both medications (Insulin and MOUNJARO) in the same container. Give yourself separate injections of insulin and MOUNJARO.
- You may give both injections in the same body area (for example, your stomach area), but not right next to each other.

Usual adult dose:

- The recommended starting dose of MOUNJARO is 2.5 mg administered subcutaneously (under the skin) once weekly. After 4 weeks your dose will go up to 5 mg once weekly. If needed, the dose may be increased by 2.5 mg after at least 4 weeks on your current dose. The maximum recommended dose is 15 mg once weekly.
- If your healthcare professional increases your dose, a new MOUNJARO (pen, vial or KwikPen) for the different dose should be used.

Overdose:

If you think you, or a person you are caring for, have taken too much MOUNJARO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

If you miss a dose and:

- it has been 4 days (96 hours) or less since you should have used MOUNJARO, use it as soon as you remember. Then inject your next dose on your usual scheduled day.
- it has been more than 4 days (96 hours) since you should have used MOUNJARO, skip the missed dose. Then inject your next dose on your usual scheduled day.

What are possible side effects from using MOUNJARO?

These are not all the possible side effects you may have when taking MOUNJARO. If you experience any side effects including side effects not listed here, tell your healthcare professional.

- Belching
- Bloating of the stomach
- Change in taste
- Constipation
- Decreased appetite
- Diarrhea
- Feeling tired
- Gas (flatulence)
- Increased heart rate
- Indigestion
- Injection site reactions – such as bruising, pain, irritation, itching, and rash
- Nausea
- Reflux or heart burn – also called gastro-esophageal reflux disease
- Stomach pain
- Unusual skin sensations - such as burning, tingling or pricking
- Vomiting

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- Weight loss

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Diabetic retinopathy (Diabetic eye disease): blurred vision, lines in vision		✓	
UNCOMMON			
Hypoglycemia (severe low blood sugar): disorientation, loss of consciousness, or seizure		✓	
RARE			
Pancreatitis: prolonged severe abdominal pain with or without vomiting		✓	✓
Dehydration that can cause sudden kidney failure: dark yellow and strong-smelling pee, feeling extremely thirsty, feeling dizzy or lightheaded		✓	✓
Sudden gallbladder problems: severe abdominal pain, yellowing of your skin, or high fever with chills		✓	✓
UNKNOWN			
Serious allergic reaction (anaphylactic reaction, angioedema): breathing problems, swelling of the throat and face, fast heartbeat		✓	✓
Malnutrition (lack of proper nutrition)**:** low vitamin, mineral, and/or protein levels, low body weight		✓	
Gastroparesis (slow stomach emptying)**:** pain, severe nausea and vomiting, prolonged belching, and prolonged bloating		✓	✓

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Ileus (slow movement of food through intestines)**:** inability to tolerate an oral diet, abdominal bloating and pain, severe nausea and vomiting		✓	✓

If you have a troublesome symptom or side effect, including symptoms or side effects that are not listed here, or a side effect becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

MOUNJARO single-dose prefilled pen and single-dose vial:

- Store MOUNJARO in a refrigerator at 2°C to 8°C.
- If needed, each single-dose prefilled pen or single-dose vial can be stored at room temperature below 30°C for up to a total of 21 days.
- Do not freeze MOUNJARO. Do not use MOUNJARO if frozen. If the pen or vial has been frozen, throw it away and use a new pen or vial.
- Store MOUNJARO in the original carton to protect from light.
- Keep out of reach and sight of children.
- The single-dose prefilled pen must be discarded after use in a puncture-resistant container.
- Throw away all opened vials after use, even if there is medicine left in the vial.

MOUNJARO KwikPen multi-dose prefilled pen:

- Store MOUNJARO KwikPen in a refrigerator at 2°C to 8°C up to the expiration date. Do not use MOUNJARO KwikPen beyond the expiration date.
- Do not freeze MOUNJARO KwikPen. Do not use MOUNJARO KwikPen if frozen.
- Protect MOUNJARO KwikPen from light.
- If needed, each multi-dose prefilled pen can be stored unrefrigerated at temperatures not to exceed 30°C for up to 30 days.
- The MOUNJARO KwikPen must be discarded after four weekly doses of tirzepatide in a puncture-resistant container or in accordance with local requirements.
- Keep out of reach and sight of children.

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If you want more information about MOUNJARO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.lilly.ca, or by calling 1-888-545-5972.

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This leaflet was prepared by Eli Lilly Canada, Inc.

Last Revised SEP 24, 2024

MOU-0005-PM-20240924

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INSTRUCTIONS FOR USE

℗MOUNJARO®

tirzepatide injection

Prefilled pen for subcutaneous use

2.5 mg/0.5 mL single-dose pen

5 mg/0.5 mL single-dose pen

7.5 mg/0.5 mL single-dose pen

10 mg/0.5 mL single-dose pen

12.5 mg/0.5 mL single-dose pen

15 mg/0.5 mL single-dose pen

Once-weekly

Important information you need to know before injecting MOUNJARO

Read this "INSTRUCTIONS FOR USE" and the Patient Medication Information before using your MOUNJARO single-dose pen and each time you get a new pen. 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 MOUNJARO the right way.

- MOUNJARO is a single-dose prefilled pen.
- One MOUNJARO single-dose prefilled pen is used 1 time each week.
- Inject under the skin (subcutaneously) only.
- You or another person can inject into your stomach (abdomen) or thigh.
- Another person should give you the injection in the back of your upper arm.

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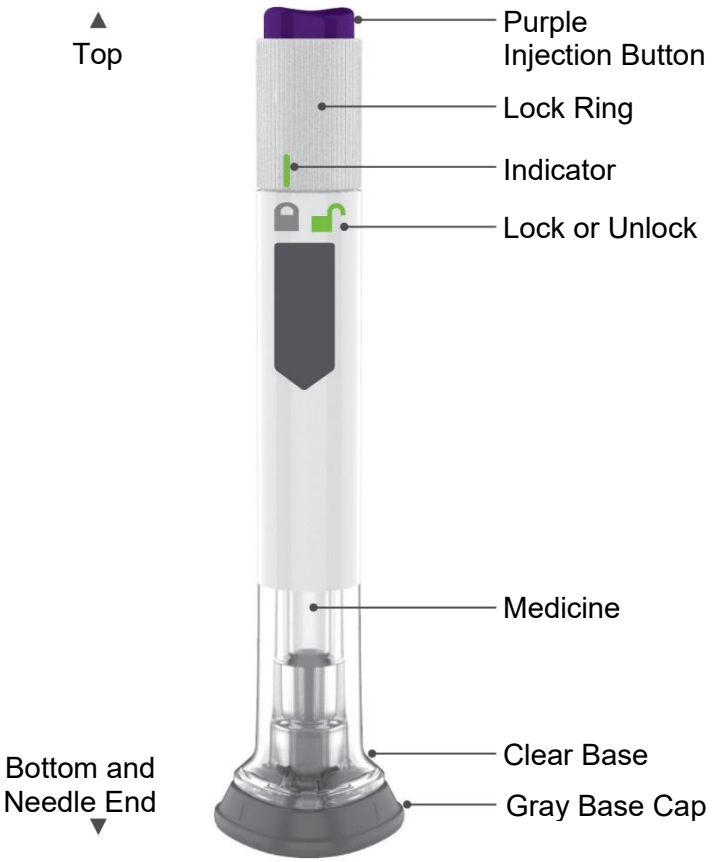
Guide to parts of MOUNJARO single-dose prefilled pen

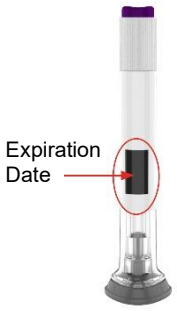


Preparing to inject MOUNJARO

Remove the Pen from the refrigerator.

Leave the gray base cap on until you are ready to inject.

Check the Pen label to make sure you have the right medicine and dose, and that it has not expired.



Inspect the Pen to make sure that it is not damaged.

Make sure the medicine in the pen is colourless to slightly yellow.

Do not use the medicine if it is: frozen, cloudy, or has particles.

Wash your hands.

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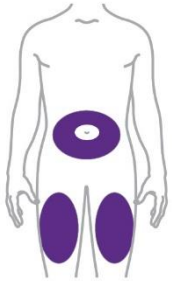
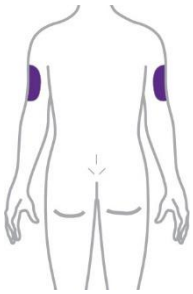
Choose your injection site

Your healthcare provider can help you choose the injection site that is best for you. Change (rotate) your injection site each week. You may use the same area of your body but be sure to choose a different injection site in that area.



You or another person can inject the medicine in your stomach (abdomen) or thigh,

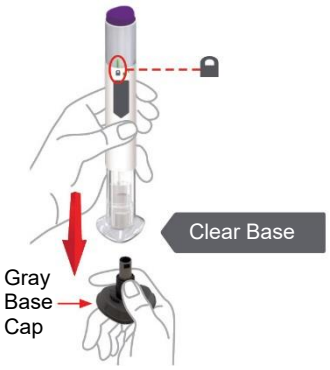
OR



Another person should give you the injection in the back of your upper arm.

Step **1**

Pull off the gray base cap



Make sure the Pen is **Locked**.

Do not unlock the Pen until you place the clear base on your skin and are ready to inject.

Pull the gray base cap straight off and throw it away in your household trash.

Do not put the gray base cap back on – this could damage the needle.

Do not touch the needle.

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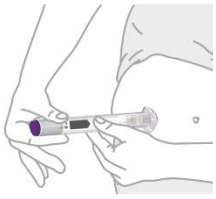
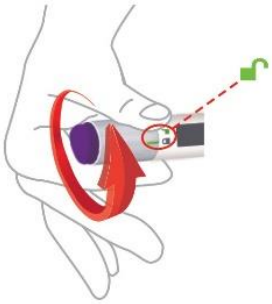
Step
2

Place Clear Base on skin, then Unlock



Place the clear base flat against your skin at the injection site. The Purple button should be away from the skin.



Unlock by turning the lock ring toward the unlock icon.

Step
3

Press and Hold up to 10 seconds

Press and Hold the purple injection button.

Listen for two loud clicks:

- First click = injection started
- Second click = injection completed

You will know your injection is complete when the gray plunger is visible.

After your injection, place the used Pen in a sharps container.

Disposing of your used Pen

- Put your used Pen in a sharps disposal container right away after use. **Do not** throw away (dispose of) Pens in your household trash.
- If you do not have a sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,

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- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local laws about how you should throw away used needles and syringes.
- **Do not** recycle your used sharps disposal container.
- Keep the disposal container out of the sight and reach of children.

Storage and handling

- Store your Pen in the refrigerator between 2°C to 8°C.
- You may store your Pen at room temperature below 30°C for up to a total of 21 days.
- **Do not** freeze your Pen. If the Pen has been frozen, throw the Pen away and use a new Pen.
- Store your Pen in the original carton to protect your Pen from light.
- The Pen has glass parts. Handle it carefully. If you drop the Pen on a hard surface, **do not** use it. Use a new Pen for your injection.
- Keep your MOUNJARO single-dose prefilled pen and all medicines out of the sight and reach of children.

Commonly asked questions

What if I see air bubbles in my Pen?

Air bubbles are normal.

What if my Pen is not at room temperature?

It is not necessary to warm the Pen to room temperature.

What if I unlock the Pen and press the purple injection button before pulling off the gray base cap?

Do not remove the gray base cap. Throw away the Pen and get a new Pen.

What if there is a drop of liquid on the tip of the needle when I remove the gray base cap?

A drop of liquid on the tip of the needle is normal. **Do not** touch the needle.

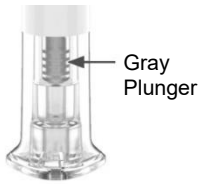
Do I need to hold the injection button down until the injection is complete?

This is not necessary, but it may help you keep the Pen steady against your skin.

I heard more than 2 clicks during my injection — 2 loud clicks and 1 soft one. Did I get my complete injection?

Some people may hear a soft click right before the second loud click. That is the normal operation of the Pen. **Do not** remove the Pen from your skin until you hear the second loud click.

I am not sure if my Pen worked the right way.



Check to see if you have received your dose. Your dose was delivered the right way if the gray plunger is visible. Also, see **Step 3** of the instructions.

If you do not see the gray plunger, contact Lilly at 1-888-545-5972 for further instructions. Until then, store your Pen safely to avoid an accidental needle stick.

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What if there is a drop of liquid or blood on my skin after my injection?

This is normal. Press a cotton ball or gauze over the injection site. **Do not** rub the injection site.

Other Information

- If you have vision problems, **do not** use your Pen without help from a person trained to use the MOUNJARO single-dose prefilled pen.

Where to learn more

- If you have questions or problems with your MOUNJARO single-dose prefilled pen, contact Lilly at 1-888-545-5972 or call your healthcare provider.
- For more information about MOUNJARO, visit our website at www.lilly.ca.

Manufactured by:
Eli Lilly Canada Inc.
P.O. Box 73
Toronto, Ontario
M5X 1B1

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MOU-0004-IFU-20240924

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INSTRUCTIONS FOR USE

PrMOUNJARO®

tirzepatide injection

single-dose vial for subcutaneous use

2.5 mg/0.5 mL single-dose vial

5 mg/0.5 mL single-dose vial

7.5 mg/0.5 mL single-dose vial

10 mg/0.5 mL single-dose vial

12.5 mg/0.5 mL single-dose vial

15 mg/0.5 mL single-dose vial

Important information you need to know before injecting MOUNJARO

Read this "INSTRUCTIONS FOR USE" and the Patient Medication Information before you start using MOUNJARO single-dose vial and each time you get a new vial. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

- MOUNJARO is a single-dose vial.
- One MOUNJARO single-dose vial is used 1 time each week.
- Inject under the skin (subcutaneously) only.
- You or another person may inject into your stomach (abdomen) or thigh.
- Another person can inject into the back of your upper arm.

Before using MOUNJARO, gather the following supplies needed to give your injection:

- 1 MOUNJARO single-dose vial
- 1 syringe and 1 needle (as recommended by your healthcare provider).
  - **Do not** reuse needles and syringes. Always use a new syringe and needle for each injection to prevent infections and blocked needles.
  - **Do not** share your needles or syringes with other people. You may give other people a serious infection or get a serious infection from them.
- 1 alcohol swab
- gauze
- 1 sharps container for throwing away used needles and syringes. See **"Disposing of used needles and syringes"** at the end of these instructions.

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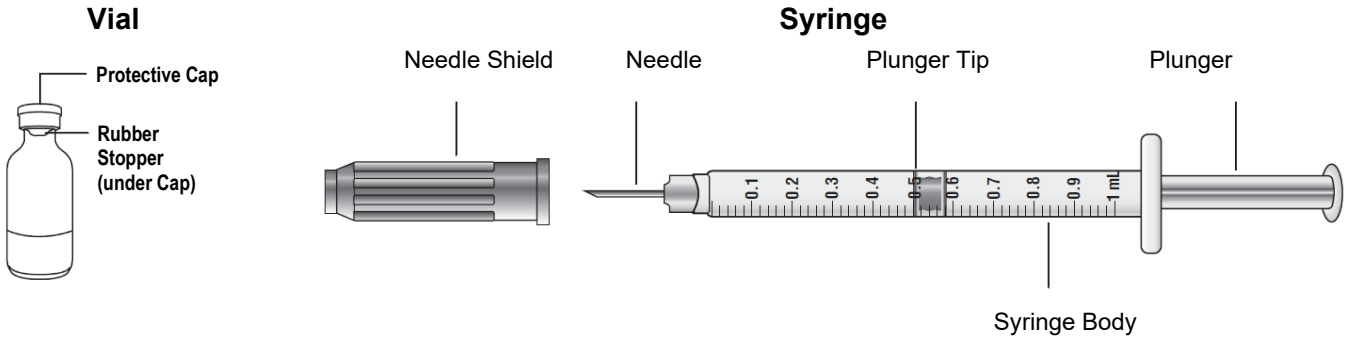
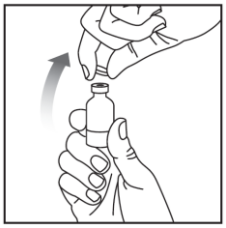
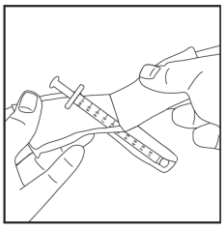


The needle and syringe shown are for illustrative purposes only. The needle and syringe recommended by your healthcare provider may look different than the needle and syringe illustrated in this INSTRUCTIONS FOR USE.

Preparing to inject MOUNJARO

- **Remove the vial** from the refrigerator.
- Wash your hands with soap and water.
- **Check the vial** label to make sure you have the right medicine and dose, and that it has not expired.
- Make sure the medicine in the vial is colourless to slightly yellow.
- **Do not** use the medicine if it is: frozen, cloudy, or has particles.

Step 1: Pull off the plastic protective cap, but **do not** remove the rubber stopper.	
Step 2: Wipe the rubber stopper with an alcohol swab.	
Step 3: Remove the outer wrapping from the syringe.	

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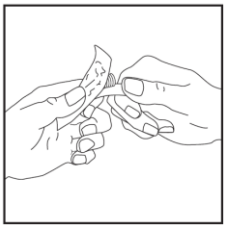
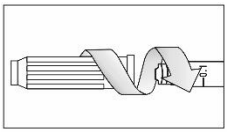
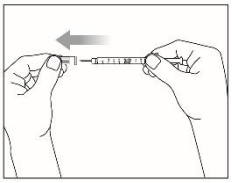
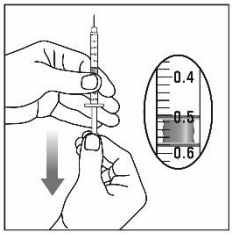
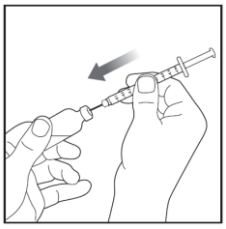
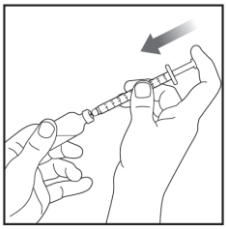
Step 4: Remove the outer wrapping from the needle. The syringe your healthcare provider recommended might have a pre-attached needle. If so, go to step 6.	
Step 5: Line up the needle with the syringe, and keep it straight as you attach it. Place the needle on top of the syringe and turn or push it on until it is tight and firmly attached, as instructed by your healthcare provider.	
Step 6: Remove the needle shield by pulling straight off. Make sure that the needle does not touch any other surfaces.	
Step 7: A. Hold the syringe with the needle pointing up. B. Pull down on the plunger until the plunger tip reaches the line on the syringe indicating that at least 0.5 mL of air has been drawn into the syringe.	
Step 8: Push the needle through the rubber stopper of the vial.	
Step 9: Push the plunger all the way in. This puts air into the vial, making it easier to pull the solution from the vial.	

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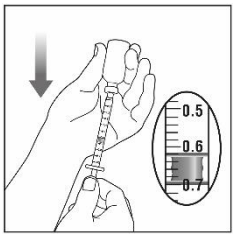
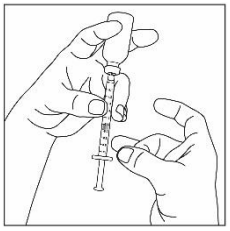
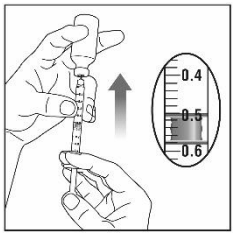
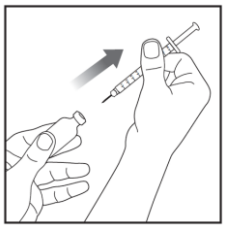
Step 10: A. Turn the vial and syringe upside down. B. Making sure the tip of the needle is in the medicine, slowly pull the plunger down until the plunger tip is past the **0.5 mL** line. C. If there are air bubbles, tap the syringe gently a few times to let any air bubbles rise to the top.	 
Step 11: Slowly push the plunger up until the plunger tip reaches the **0.5 mL** line. At this point, there should be no air in the syringe.	
Step 12: Pull the syringe out of the rubber stopper of the vial. Make sure to pull the syringe straight out to avoid bending the needle. Make sure that the needle does not touch any other surfaces.	

Injecting MOUNJARO

- Inject exactly as your healthcare provider has shown you.
- Change (rotate) your injection site within the area you choose for each dose. You may use the same area of your body but be sure to choose a different injection site within that area. Changing the injection site reduces your risk of developing the following conditions at the injection site:
  - Getting lipodystrophy (pits in skin or thickened skin) and
  - localized cutaneous amyloidosis (skin with lumps).
- **Do not** inject where the skin has pits, is thickened, or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- **Do not** mix MOUNJARO with any other medicine.
- **Do not** inject MOUNJARO in the same injection site used for other medicines.

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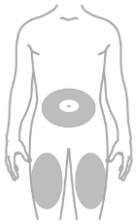
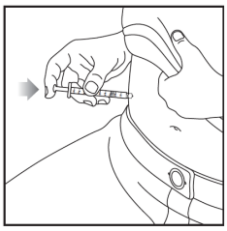
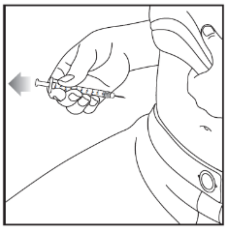
Step 13: Choose your injection site. Prepare the injection site as directed by your healthcare provider. MOUNJARO is injected under the skin (subcutaneously). • You or another person can inject the medicine in your stomach (abdomen) or thigh. OR • Another person can give you the injection in the back of your upper arm.	 OR
Step 14: Insert the needle into your skin.	
Step 15: Push down on the plunger to inject your full dose. • The plunger tip should be at the bottom of the syringe. • The needle should stay in your skin for at least 5 seconds to make sure you have injected all of your medicine.	
Step 16: Pull the needle out of your skin. • If you see blood after you take the needle out of your skin, press the injection site with a piece of gauze or an alcohol swab. **Do not** rub the area. • **Do not** recap the needle. Recapping the needle can lead to a needle stick injury.	

Disposing of your used vial, needles and syringes

- Put your used needle and syringe in a sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and syringes in your household trash.
- If you do not have a sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,

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- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local laws about how you should throw away used needles and syringes.
- Throw away all opened vials after use, even if there is medicine left in the vial.
- **Do not** recycle your used sharps disposal container.

Storing and handling

- Store all unopened vials in the refrigerator at 2°C to 8°C.
- You may store the unopened vial at room temperature below 30°C for up to a total of 21 days.
- **Do not** freeze. **Do not** use if MOUNJARO has been frozen.
- Store the vial in the original carton to protect from light.

Keep your MOUNJARO vials, syringes, needles, and all medicines out of the sight and reach of children.

Where to learn more

- If you have any questions or problems with your MOUNJARO single-dose vial, contact Lilly at 1-888-545-5972 or call your healthcare provider for help.
- For more information about MOUNJARO, visit our website at www.lilly.ca.

Manufactured by

Eli Lilly Canada Inc.
P.O. Box 73
Toronto, Ontario
M5X 1B1

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Instructions for Use revised: SEP 24, 2024

MON-VL-0003-IFU-20240924

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INSTRUCTIONS FOR USE

PrMOUNJARO® KwikPen®

tirzepatide injection

Single-patient-use prefilled pen for subcutaneous use

Each pen contains 4 fixed doses, one dose taken weekly.

2.5 mg/0.6 mL multi-dose pen

5 mg/0.6 mL multi-dose pen

7.5 mg/0.6 mL multi-dose pen

10 mg/0.6 mL multi-dose pen

12.5 mg/0.6 mL multi-dose pen

15 mg/0.6 mL multi-dose pen

Important information you need to know before injecting MOUNJARO KwikPen

Read this "INSTRUCTIONS FOR USE" and the Patient Medication Information before using your MOUNJARO KwikPen multi-dose prefilled pen and each time you get a new KwikPen. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

- MOUNJARO KwikPen is a multi-dose single-patient-use prefilled pen.
- **One MOUNJARO KwikPen contains 4 fixed doses of 0.6 mL, one dose taken weekly.**
- Inject 0.6 mL in a single weekly injection, under the skin (subcutaneously) only.
- After 4 doses covering a month's treatment, throw away (discard) the KwikPen, including the unused medication. The KwikPen will prevent you from dialing a full dose after you have given yourself 4 weekly doses.
- **Do not** transfer solution from your MOUNJARO KwikPen into a syringe. **Do not** inject the leftover medication.

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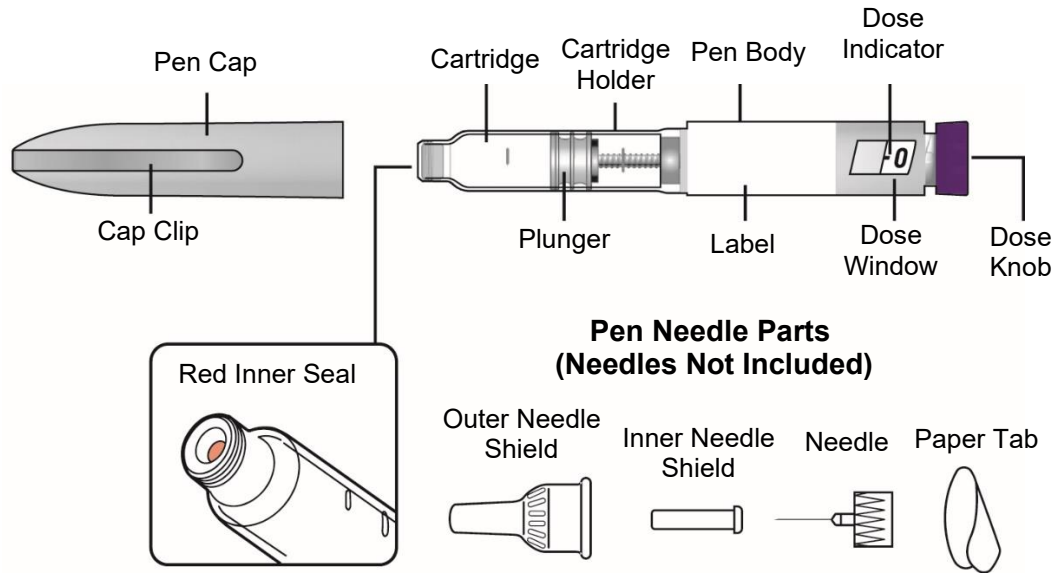
- **Do not** share your MOUNJARO KwikPen with other people, even if the pen needle has been changed. You may give other people a serious infection or get a serious infection from them.
- People who are blind or have vision problems should not use the KwikPen without help from a person trained to use the KwikPen.

Guide to parts

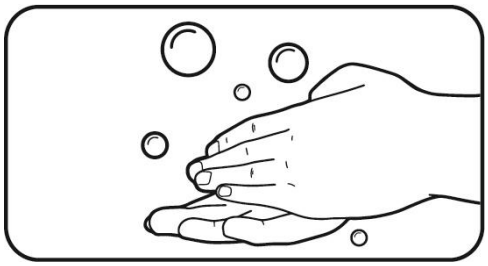
Parts of the MOUNJARO multi-dose prefilled pen (KwikPen)



Supplies needed to give your injection

- 1 MOUNJARO KwikPen multi-dose prefilled pen
- 1 pen needle (as recommended by your healthcare provider)
- Alcohol swab
- Gauze or cotton ball
- Sharps disposal container or household container

Preparing to inject MOUNJARO KwikPen



Step 1:

- Wash your hands with soap and water.

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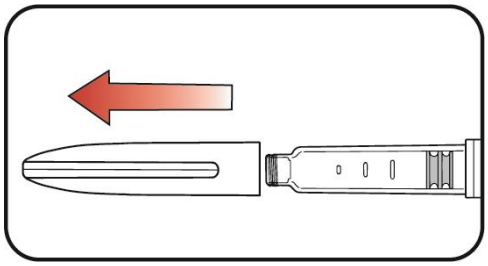
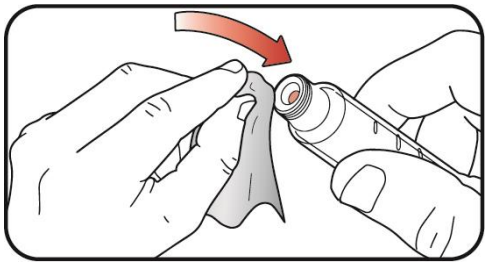


Step 2:

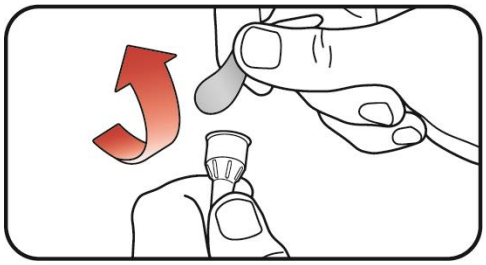
- Pull the KwikPen cap straight off.
- Inspect the KwikPen and label. **Do not** use if:
  - the medication name or dose strength does not match your prescription.
  - the KwikPen is expired (EXP) or looks damaged.
  - the medication has been frozen, has particles, is cloudy, or is discolored.

Make sure the medicine in the KwikPen is colourless to slightly yellow.



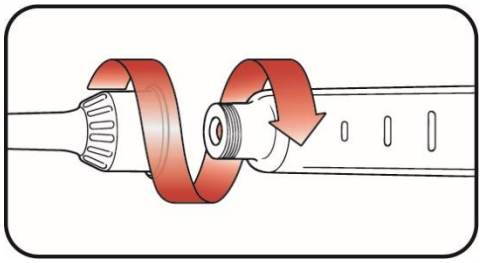
Step 3:

- Wipe the red inner seal with an alcohol swab.



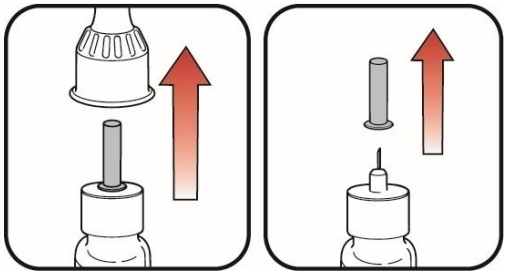
Step 4:

- **Select a new pen needle.** Always use a new pen needle for each injection to help prevent infections and blocked needles.
- Pull off the paper tab from the outer needle shield.



Step 5:

- Push the capped pen needle straight onto the KwikPen and twist the pen needle on until it is tight.



a. Outer needle shield **b. Inner needle shield**

Step 6:

a. Pull off the outer needle shield and keep it. This will be reused.

b. Pull off the inner needle shield. Put it in your household trash.

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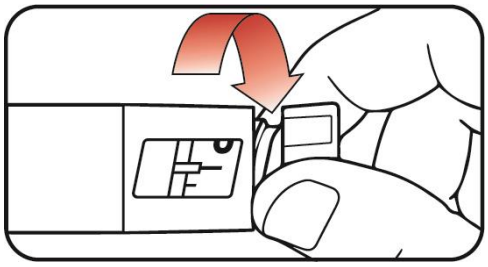
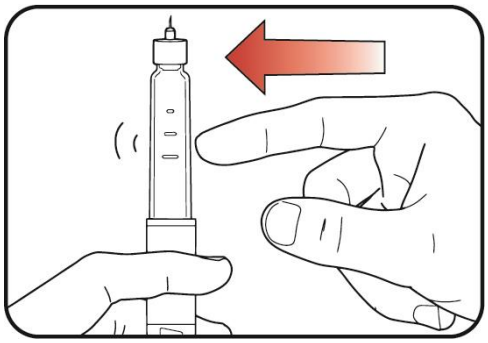


Step 7:

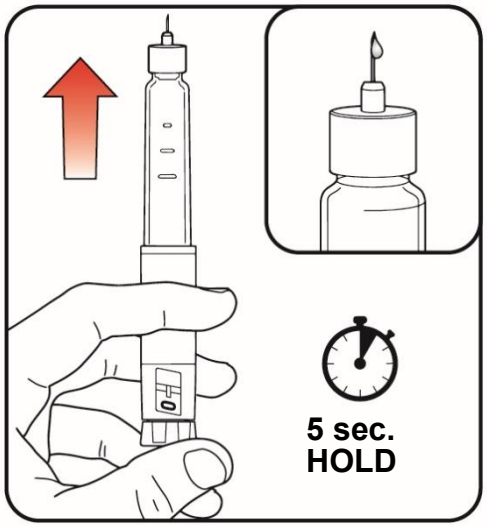
- Slowly turn the dose knob until you hear **2 clicks** and the extended line shown in the dose window aligns with the dose indicator. This is the prime position.

  It can be corrected by turning the dose knob in either direction until the prime position is achieved.



Step 8:

- Hold your KwikPen with the needle pointing up.
- Tap the cartridge holder gently to collect air bubbles at the top.



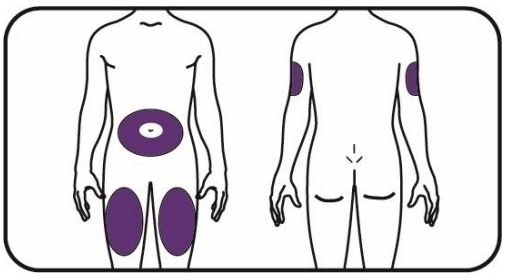
Step 9:

- Prime your KwikPen. To do this, **push and hold the dose knob in** until it stops, and the icon is shown in the dose window. **Hold the dose knob in and slowly count to 5.** This will release some medicine into the air. **Do not** inject into your body.

  Priming removes air from the cartridge and makes sure that your KwikPen is working correctly. Your KwikPen has been primed if a small amount of medicine comes out of the tip of the pen needle.

  – If you do not see medicine at the tip of the needle, repeat **steps 7-9**, no more than 2 additional times.
  – If you still do not see medicine, then change the pen needle and repeat **steps 7-9,** no more than 1 additional time.
  – If you still do not see medicine, contact Lilly at 1-888-545-5972.

Injecting MOUNJARO KwikPen



a. Front **b. Back**

Step 10:

- Choose an injection site.
  a. You or another person can inject the medicine in your thigh or stomach (abdomen) at least 5 centimeters from the belly button (see the image).
  b. Another person should give you the injection in the back of your upper arm.
- **Change (rotate)** your injection site each week. You may use the same area of your body but be sure to choose a different injection site in that area.

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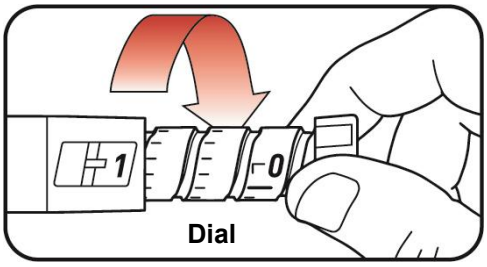
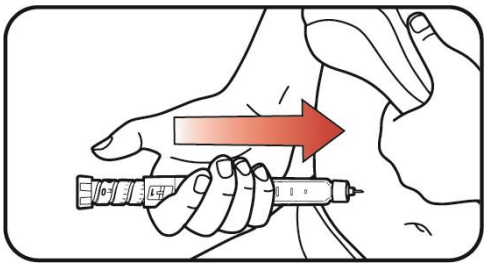


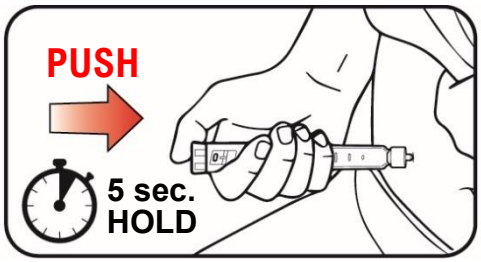
Step 11:

- Turn the dose knob until it stops and the 1 icon is shown in the dose window. **The 1 icon is equal to a full dose (0.6 mL).**

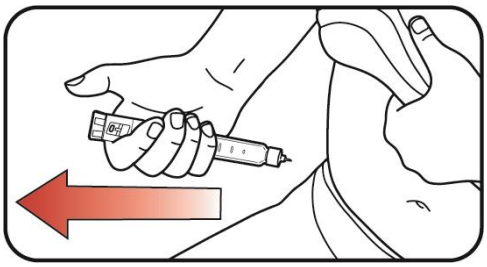


Step 12:

a. Insert the needle into your skin.



b. Inject the medicine by **pushing the dose knob in** until it stops. **Hold the dose knob in and slowly count to 5.** The 0 icon must be shown in the dose window before removing the needle.



Step 13:

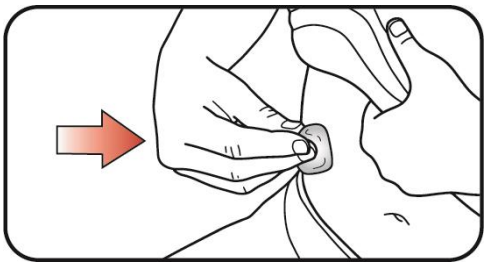
- Pull the needle out of your skin. A drop of medicine on the needle tip is normal. It will not affect your dose.
- Confirm the 0 icon is in the dose window.

  If you see the 0 icon in the dose window, you have received the full dose.

  If you do not see the 0 icon in the dose window, insert the needle back into your skin and finish your injection. **Do not** turn the dose knob back to the 1 icon.

  If you still do not think you received the full dose, **do not** start over or repeat the injection. Contact Lilly at 1-888-545-5972.

After your MOUNJARO KwikPen injection



Step 14:

- If you see blood after you pull the needle out of your skin, lightly press the injection site with gauze or a cotton ball.

  Do not rub the injection site.

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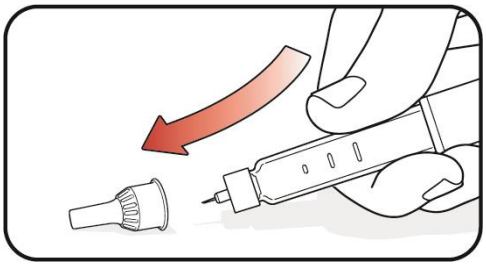
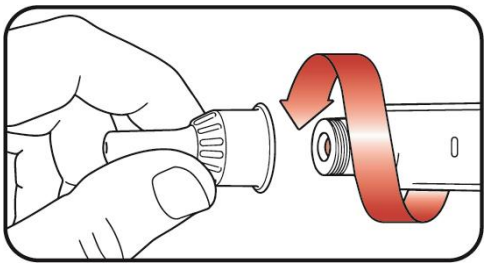


Step 15:

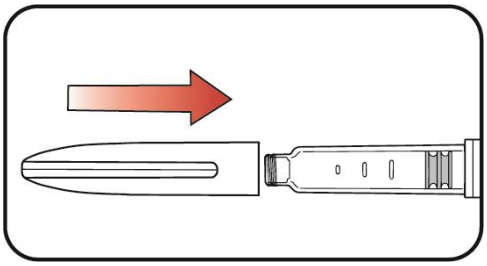
- Carefully replace the outer needle shield.



Step 16:

- Unscrew the capped needle and put the needle in a sharps container (see "Disposing of MOUNJARO KwikPen and needles" section).

  Do not store the KwikPen with the needle attached to prevent leaking, blocking the needle, and air from entering the KwikPen.



Step 17:

- Replace the KwikPen cap.

  Do not store the KwikPen without the pen cap attached.

Storing your MOUNJARO KwikPen

Unused KwikPen:

- Store **unused KwikPen** in the **refrigerator** between 2°C to 8°C.
- Unused KwikPen may be used until the expiration date printed on the label if the KwikPen has been kept in the refrigerator.
- **Do not** freeze your KwikPen. Throw away (discard) the KwikPen if it has been frozen.

Used KwikPen:

- You may store your **used KwikPen** at **room temperature** up to 30°C for up to 30 days.
- Keep away from heat and light.
- Keep your KwikPen and needles out of the sight and reach of children.
- Throw away the KwikPen 30 days after first use even though the KwikPen has medication left in it.
- Throw away the KwikPen after receiving the 4 weekly doses contained in the pen. Attempting to inject any leftover medicine could result in an incomplete dose even though the KwikPen still has medication left in it.

Disposing of MOUNJARO KwikPen and needles

- Put your used pen needles in a sharps disposal container right away after use.
- **Do not** throw away (discard) loose pen needles in your household trash.
- Discard the used KwikPen in a sharps disposal container after you have removed the needle.
- If you do not have a sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,

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  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local laws about how you should throw away used needles.
- Do not recycle your used sharps disposal container.

Troubleshooting

- If you cannot remove the KwikPen cap, gently twist the KwikPen cap back and forth, and then pull the KwikPen cap straight off.
- If the dose knob is hard to push:
  - pushing the dose knob more slowly will make it easier to inject.
  - your needle may be blocked. Put on a new pen needle and prime the KwikPen.
  - you may have dust, food, or liquid inside the KwikPen. Throw the KwikPen away and get a new KwikPen.

Additional Information:

QR CODE

Scan this code or visit www.mounjaro.ca for instructions on how to use MOUNJARO KwikPen.

For more information, please contact Eli Lilly Canada Incorporated at 1-888-545-5972 or visit the website at www.lilly.ca.

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Medication Calendar

Use MOUNJARO KwikPen 1 time a week.

Write the day of the week you choose to inject.
Inject on this day each week (Example: Monday).

I inject my weekly 0.6 mL dose on the dates below.

(Month/Day) (Month/Day) (Month/Day) (Month/Day)

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