▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – MOUNJARO (TIRZEPATIDE) SOLUTION FOR INJECTION – PRE-FILLED PEN [AUTOINJECTOR]

1 NAME OF THE MEDICINE

Tirzepatide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MOUNJARO tirzepatide 2.5 mg/0.5 mL solution for injection pre-filled pen [autoinjector]

Each pre-filled pen contains tirzepatide 2.5 mg in 0.5 mL solution.

MOUNJARO tirzepatide 5 mg/0.5 mL solution for injection pre-filled pen [autoinjector]

Each pre-filled pen contains tirzepatide 5 mg in 0.5 mL solution.

MOUNJARO tirzepatide 7.5 mg/0.5 mL solution for injection pre-filled pen [autoinjector]

Each pre-filled pen contains tirzepatide 7.5 mg in 0.5 mL solution.

MOUNJARO tirzepatide 10 mg/0.5 mL solution for injection pre-filled pen [autoinjector]

Each pre-filled pen contains tirzepatide 10 mg in 0.5 mL solution.

MOUNJARO tirzepatide 12.5 mg/0.5 mL solution for injection pre-filled pen [autoinjector]

Each pre-filled pen contains tirzepatide 12.5 mg in 0.5 mL solution.

MOUNJARO tirzepatide 15 mg/0.5 mL solution for injection pre-filled pen [autoinjector]

Each pre-filled pen contains tirzepatide 15 mg in 0.5 mL solution.

For the full list of excipients, see section **6.1 List of excipients**.

3 PHARMACEUTICAL FORM

Solution for Injection.

MOUNJARO is a clear, colourless to slightly yellow, preservative-free, sterile solution for subcutaneous administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Type 2 Diabetes Mellitus:

MOUNJARO is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is not tolerated or contraindicated.
- in addition to other medicinal products for the treatment of type 2 diabetes.

4.2 DOSE AND METHOD OF ADMINISTRATION

Use in Adults (≥ 18 years)

The starting dose of tirzepatide is 2.5 mg once weekly.

After 4 weeks, increase the dose to 5 mg once weekly.
If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose.

The recommended doses are 5 mg, 10 mg and 15 mg.

The 2.5 mg, 7.5 mg and 12.5 mg are not maintenance doses.

The maximum dose of tirzepatide is 15 mg once weekly.

Available doses are 2.5mg, 5mg, 7.5mg, 10mg, 12.5mg and 15mg. (see Section **2 Qualitative and Quantitative Composition**)

Self-monitoring of blood glucose is not needed in order to adjust the dose of tirzepatide.

When tirzepatide is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued.

When tirzepatide is added to existing therapy of a sulfonylurea and/or insulin, a reduction in the dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin. A stepwise approach to insulin reduction is recommended. (see sections **4.4 Special warnings and precautions for use** and **4.8 Adverse effects (Undesirable effects)**).

Missed dose

If a dose is missed, it should be administered as soon as possible.

If there are fewer than 3 days until the next regularly scheduled dose, skip the missed dose and administer the next dose on the regularly scheduled day. Patients can then resume their regular once weekly dosing schedule.

Changing the 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).

Special population

Use in the elderly (≥ 65 years)

No dose adjustment is needed based on age.

Gender and body weight

No dose adjustment is needed based on gender or body weight.

Race and Ethnicity

No dose adjustment is needed based on race and ethnicity.

Renal impairment

No dose adjustment is needed in patients with renal impairment (including end-stage renal disease). Experience with the use of tirzepatide in patients with severe renal impairment and ESRD is limited. Caution should be exercised when treating these patients with tirzepatide.

Hepatic impairment

No dose adjustment is needed in patients with hepatic impairment. Experience with the use of tirzepatide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with tirzepatide.

Paediatric population

The safety and efficacy of tirzepatide in children aged less than 18 years have not yet been established. No data are available.

Method of Administration

MOUNJARO can be injected at any time of the day, with or without meals.

Inject tirzepatide subcutaneously in the abdomen, thigh or upper arm. Product is for single use in one patient only.

It is recommended to rotate injection sites with each dose.

4.3 CONTRAINDICATIONS

MOUNJARO is contraindicated in patients with known hypersensitivity to tirzepatide or any of the excipients listed in section **6.1 List of excipients**.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

MOUNJARO should not be used in patients with Type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Acute pancreatitis

Tirzepatide has not been studied in patients with a history of pancreatitis and should be used in caution with these patients.

Acute pancreatitis has been reported in patients treated with tirzepatide.

Patients should be informed of the symptoms of acute pancreatitis. If pancreatitis is suspected, tirzepatide should be discontinued. If the diagnosis of pancreatitis is confirmed, tirzepatide should not be restarted. In the absence of other signs and symptoms of pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Hypoglycaemia

Patients receiving tirzepatide in combination with an insulin secretagogue (for example, a sulfonylurea) or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of the insulin secretagogue or insulin (see sections **4.2 Dose and method of administration** and **4.8 Adverse effects (Undesirable effects)**).

Gastrointestinal effects

Tirzepatide has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhoea (see section **4.8 Adverse effects (Undesirable effects)**). These events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure.

Patients treated with tirzepatide should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Monitor renal function when initiating or escalating doses of MOUNJARO in patients with renal impairment reporting severe gastrointestinal adverse reactions.

Severe gastrointestinal disease

Tirzepatide has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and should be used with caution in these patients.

Diabetic retinopathy

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

Congestive Heart Failure

There is limited therapeutic experience in patients with congestive heart failure.

Use in hepatic impairment

No dose adjustment is needed in patients with hepatic impairment (see section **5.2 Pharmacokinetic properties**). Experience with the use of tirzepatide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with tirzepatide.

Use in renal impairment

No dose adjustment is needed in patients with renal impairment (including end-stage renal disease) (see section **5.2 Pharmacokinetic properties**). Experience with the use of tirzepatide in patients with severe renal impairment and ESRD is limited. Caution should be exercised when treating these patients with tirzepatide.

Use in the elderly

No dose adjustment is required based on age. Only very limited data are available from patients aged ≥ 85 years.

Paediatric use

The safety and efficacy of tirzepatide in children aged less than 18 years have not yet been established. No data are available.

Effects on laboratory tests

No information on the effect of tirzepatide on laboratory tests is available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Tirzepatide delays gastric emptying and has the potential to affect the rate of absorption of concomitantly administered oral medications. This effect, resulting in decreased C_{max} and a delayed t_{max}, is most pronounced at the time of tirzepatide treatment initiation.

Based on the results from a study with paracetamol, which was used as a model medicinal product to evaluate the effect of tirzepatide on gastric emptying, it is not anticipated that tirzepatide treatment will result in a clinically meaningful impact on orally administered drugs that do not have a narrow therapeutic index. However, it is recommended to monitor patients on oral medicinal products with a narrow therapeutic index (e.g., warfarin, digoxin), especially during the early phase of treatment with tirzepatide and

following any dose increase. The risk of delayed effect should also be considered for any oral medicinal product for which a rapid onset of effect is important.

Oral contraceptives

Administration of a combination oral contraceptive (0.035 mg ethinylestradiol 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 area under the curve (AUC) and a delay in t_{max} of 2.5 to 4.5 hours. This reduction in exposure after a single 5 mg dose of tirzepatide is not considered clinically relevant. Doses other than a single 5 mg dose of tirzepatide were not investigated in this interaction study.

The reduction in exposure described above may be significant in a setting with concomitant administration of medicines also affecting those exposures. Appropriate contraception methods (including non-oral contraceptives) should be discussed with the patient based on the patient's individual circumstances prior to commencing tirzepatide.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of tirzepatide on fertility in humans is unknown.

Tirzepatide did not affect fertility in male rats at doses up to 3 mg/kg/day, resulting in exposures 2 times the clinical AUC at the maximum recommended human dose (MRHD). In female rats, prolonged oestrus cycling and decreases in the mean numbers of corpora lutea, implantation sites, and viable embryos per litter was observed at subclinical exposures based on AUC at the MRHD.

Use in pregnancy

Pregnancy Category D.

There are no adequate and well-controlled studies of tirzepatide in pregnant women. Tirzepatide should not be used during pregnancy. Women of childbearing potential are advised to use contraception during treatment with tirzepatide (see **Section 4.5 Interactions with other medicines and other forms of interactions**). If a patient wishes to become pregnant or becomes pregnant, treatment with tirzepatide should be discontinued.

Studies in animals have shown reproductive toxicity when tirzepatide was administered during organogenesis. In pregnant rats, embryofetal toxicity (increased post-implantation loss, impaired growth and an increased incidence of fetal abnormalities) was observed at subclinical plasma exposures. All developmental effects occurred at maternally toxic doses. Exposures at the No Observed Adverse Effects Level (NOAEL) were subclinical and a direct effect of tirzepatide on the fetus cannot be excluded.

Use in lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. When tirzepatide is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see section **4.4 Special warnings and precautions for use**).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

In 7 completed phase 3 studies, 5,119 patients were exposed to tirzepatide alone or in combination with other glucose lowering medicinal products. The most frequently reported adverse reactions in clinical studies were gastrointestinal disorders, including nausea (very common), diarrhoea (very common), and vomiting (common). In general, these reactions were mostly mild or moderate in severity and occurred more often during dose escalation and decreased over time. (see sections **4.2 Dose and method of administration**, **4.4 Special warnings and precautions for use**).

Tabulated list of adverse reactions

The following related adverse reactions have been identified and are listed in **Table 1** as MedDRA preferred term by system organ class and in order of decreasing incidence (very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥ 1/10,000 to < 1/1,000; very rare: < 1/10,000) and not known (cannot be estimated from the available data). Within each incidence grouping, adverse reactions are presented in order of decreasing frequency.

Table 1 Adverse reactions

System Organ Class Preferred Term	**Very Common ≥10%**	**Common ≥1% and <10%**	**Uncommon ≥0.1% and <1%**	**Rare ≥0.01% and <0.1%**	**Very Rare <0.01%**
Gastrointestinal Disorders					
Nausea	X				
Diarrhoea[a]	X				
Abdominal Pain[a]		X			
Vomiting		X			
Dyspepsia		X			
Constipation[a]		X			
Abdominal Distension		X			
Eructation		X			
Flatulence		X			
Gastroesophageal Reflux Disease		X			
Cholelithiasis			X		
Acute Pancreatitis			X		
General Disorders and Administration Site Conditions					
Fatigue[a]		X			
Injection Site Reaction[a]		X			

System Organ Class Preferred Term	**Very Common ≥10%**	**Common ≥1% and <10%**	**Uncommon ≥0.1% and <1%**	**Rare ≥0.01% and <0.1%**	**Very Rare <0.01%**
Immune System Disorders					
Hypersensitivity		X			
Metabolism and Nutrition Disorders					
Decreased Appetite		X			
Hypoglycaemia[b]					
Hypoglycaemia with concomitant secretagogues/insulin					
-add on to basal insulin, with or without metformin	X				
-add on to sulfonylurea, with or without metformin and/or SGLT-2i[c]	X				
Hypoglycaemia without concomitant secretagogues/insulin					
- add on to metformin and SGLT2i[c]		X			
- add on to metformin			X		

[a] **Includes the following MedDRA preferred terms**:
Diarrhoea: diarrhoea, frequent bowel movements
Abdominal Pain: abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, gastrointestinal pain
Constipation: constipation, faeces hard
Fatigue: fatigue, asthenia, malaise, lethargy
Injection Site Reaction: injection site reaction, injection site erythema, injection site pruritus, injection site bruising, injection site hypersensitivity, injection site pain, injection site haemorrhage, injection site irritation, injection site rash, injection site dermatitis, injection site eczema, injection site mass, injection site oedema, injection site swelling.
[b] hypoglycaemia with blood glucose <3.0 mmol/L or severe hypoglycaemia
[c] sodium-glucose co-transporter 2 inhibitor

Table 2 Summary of treatment-emergent adverse events with frequency ≥5% in any treatment group

Preferred Term	**TZP 5 mg (N=237) %**	**TZP 10 mg (N=240) %**	**TZP 15 mg (N=241) %**	**TZP ALL (N=718) %**	**Placebo (N=235) %**
Nausea	12.2	15.4	18.3	15.3	4.3
Diarrhoea	11.8	13.3	16.2	13.8	8.9
Nasopharyngitis	10.5	6.7	9.5	8.9	14.0
Decreased Appetite	5.5	9.6	11.2	8.8	1.3
Dyspepsia	8.0	7.5	5.4	7.0	2.6
Vomiting	5.1	5.0	9.1	6.4	2.1
Constipation	5.9	5.8	6.6	6.1	1.3
Lipase increased	3.0	1.3	5.4	3.2	2.6
Hypergycaemia	2.5	2.1	1.7	2.1	20.0

N=number of patients in treatment group; TZP=tirzepatide

Description of selected adverse reactions

Gastrointestinal adverse reactions

In the placebo-controlled phase 3 studies, gastrointestinal disorders were dose-dependently increased for tirzepatide 5 mg (37.1%), 10 mg (39.6%) and 15 mg (43.6%)

compared with placebo (20.4%). Nausea occurred in 12.2%, 15.4% and 18.3% versus 4.3% and diarrhoea in 11.8%, 13.3% and 16.2% versus 8.9% for tirzepatide 5 mg, 10 mg and 15 mg versus placebo. Gastrointestinal adverse reactions were mostly mild (74%) or moderate (23.3%) in severity. The incidence of nausea, vomiting, and diarrhoea was higher during the dose escalation period and decreased over time.

More subjects in the tirzepatide 5 mg (3.0%), 10 mg (5.4%) and 15 mg (6.6%) groups compared to the placebo group (0.4%) discontinued permanently due to the gastrointestinal event.

Hypoglycaemia

The risk of severe hypoglycaemia with tirzepatide is low. In clinical studies, 10 (0.20%) patients reported 12 episodes of severe hypoglycaemia. Of these 10 patients, 5 (0.10%) were on a background of insulin glargine or sulfonylurea who reported 1 episode each.

Clinically significant hypoglycaemia occurred in 10 to 14% (0.14 to 0.16 events/patient year) of patients when tirzepatide was added to sulfonylurea and in 14 to 19% (0.43 to 0.64 events/patient year) of patients when tirzepatide was added to basal insulin.

The rate of clinically significant hypoglycaemia when tirzepatide was used as monotherapy or when added to other oral antidiabetic medication was up to 0.03 events/patient year (see **Table 1** and sections **4.2 Dose and method of administration**, **4.4 Special warnings and precautions for use** and **5.1 Pharmacodynamic properties**).

Hypersensitivity reactions

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

Immunogenicity

There was no evidence of an altered pharmacokinetic profile or an impact on efficacy and safety associated with the development of anti-drug antibodies (ADAs).

Consistent with the potentially immunogenic properties of protein and peptide medicinal products, patients may develop antibodies following treatment with tirzepatide.

Across seven Phase 3 clinical studies, 2,570 (51.1%) tirzepatide-treated patients developed ADAs. Of the overall tirzepatide-treated patients, 1.9% and 2.1% had neutralising antibodies against tirzepatide activity on the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, respectively. 0.9% and 0.4% had neutralising antibodies against native GIP and GLP-1, respectively.

Heart rate

In the placebo-controlled phase 3 studies, treatment with tirzepatide resulted in a maximum mean increase in heart rate of 3 to 5 beats per minute. The maximum mean increase in heart rate in placebo-treated patients was 1 beat per minute.

The incidence of patients who had a change of baseline heart rate of >20 bpm for 2 or more consecutive visits was 2.1%, 3.8% and 2.9%, for tirzepatide 5 mg, 10 mg and 15 mg, respectively, compared with 2.1% for placebo.

Small mean increases in PR interval were observed with tirzepatide when compared to placebo (mean increase of 1.4 to 3.2 msec and mean decrease of 1.4 msec respectively). No difference in arrythmia and cardiac conduction disorder treatment emergent events were observed between tirzepatide 5 mg, 10 mg, 15 mg and placebo (3.8%, 2.1%, 3.7% and 3% respectively).

Injection site reactions

In the placebo-controlled phase 3 studies, injection site reactions were increased for tirzepatide (3.2%) compared with placebo (0.4%).

Overall, in the phase 3 studies, the most common signs and symptoms of injection site reactions were erythema and pruritus. The maximum severity of injection site reactions for patients was mild (90%) or moderate (10%). No injection site reactions were serious.

Pancreatic enzymes

In the placebo-controlled phase 3 studies, treatment with tirzepatide resulted in mean increases from baseline in pancreatic amylase of 33% to 38% and lipase of 31% to 42%. Placebo treated patients had an increase from baseline in amylase of 4% and no changes were observed in lipase.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In the event of overdose, appropriate supportive treatments should be initiated according to the patient's clinical signs and symptoms. A period of observation and treatment of these symptoms may be necessary, taking into account the half-life of tirzepatide (approximately 5 days).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins,

ATC code: not yet assigned.

Mechanism of action

Tirzepatide is a long-acting dual GIP and GLP-1 receptor agonist. It is a 39-amino acid peptide with a C20 fatty diacid moiety that enables albumin binding and prolongs half-life. Both receptors are present on the pancreatic α and β endocrine cells, brain, heart, vasculature, immune cells (leukocytes), gut and kidney. GIP receptors are also present on adipocytes.

Tirzepatide is selective to human GIP and GLP-1 receptors. Tirzepatide has high affinity to both the 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. Tirzepatide is a biased agonist at the GLP-1 receptor with preferential signaling towards the activation of adenylyl cyclase as opposed to the recruitment of β - arrestin.

Pharmacodynamic effects

Glycaemic control

Tirzepatide improves glycaemic control by lowering fasting and postprandial glucose concentrations in patients with type 2 diabetes through several mechanisms.

Insulin secretion

Tirzepatide increases β - cell glucose sensitivity. In a hyperglycaemic clamp study in patients with type 2 diabetes, tirzepatide was compared to placebo and the selective GLP-1 receptor agonist semaglutide 1mg for insulin secretion. Tirzepatide 15 mg enhanced the first- and second-phase insulin secretion rate by 466% and 302% from baseline, respectively, in a glucose dependent manner. There was no change in first- and second-phase insulin secretion rate for placebo and the rates increased for semaglutide 1 mg by 298% and 223%, respectively.

Insulin sensitivity

Tirzepatide 15 mg improved whole body insulin sensitivity by 63%, as measured by M-value, a measure of glucose tissue uptake using hyperinsulinemic euglycaemic clamp. The M-value was unchanged for placebo and increased in semaglutide 1 mg by 35%.

Tirzepatide lowers body weight in patients with type 2 diabetes, which may contribute to improvement in insulin sensitivity. Reduced food intake with tirzepatide contributes to body weight loss. Body weight reduction is mostly due to reduced fat mass.

Glucagon concentration

Tirzepatide reduced the fasting and postprandial glucagon concentrations. Tirzepatide 15 mg reduced fasting glucagon concentration by 28% and glucagon AUC after a mixed meal by 43%, compared with no change for placebo, and decreases for semaglutide 1mg in fasting glucagon by 22% and in glucagon AUC by 29%.

Gastric emptying

Tirzepatide delays gastric emptying, with largest delay after the first dose. and this effect diminishes over time. Slowing post-meal glucose absorption and can lead to a beneficial effect on postprandial glycaemia.

Energy intake

In patients with type 2 diabetes, tirzepatide reduced food intake contributing to body weight loss. In pre-clinical rodent studies tirzepatide induced a preference to lower fat food.

Clinical trials - Clinical efficacy and safety

Glycaemic control and body weight

The safety and efficacy of tirzepatide were evaluated in five (5) global randomised, controlled, phase 3 studies (SURPASS 1 to 5) assessing glycaemic efficacy as the primary objective involving 6,263 treated patients with type 2 diabetes (4,199 treated with tirzepatide). The secondary objectives included body weight, fasting serum glucose (FSG) and proportion of patients reaching target HbA1c. All five phase 3 studies assessed tirzepatide 5 mg, 10 mg and 15 mg. All patients treated with tirzepatide started with 2.5 mg for 4 weeks. Then the dose of tirzepatide was increased by 2.5 mg every 4 weeks until they reached their assigned dose.

Across all studies, treatment with tirzepatide demonstrated sustained, statistically significant and clinically meaningful reductions from baseline in HbA1c and body weight compared to either placebo or active control treatment (semaglutide, insulin degludec and insulin glargine) for up to 1 year. In 1 study these effects were sustained for up to 2 years. Results from the phase 3 studies are presented below based on the modified intent-to-treat (mITT) population consisting of all randomly assigned patients who were exposed to at least 1 dose of study treatment, excluding patients discontinuing study treatment due to inadvertent enrolment. The analysis aligned to the efficacy estimand for a longitudinal continuous variable employed a mixed model for repeated measurements.

SURPASS 1 – Monotherapy

In a 40-week double blind placebo-controlled study (GPGK), 478 patients with inadequate glycaemic control with diet and exercise, were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or placebo. Patients had a mean age of 54 years and 52 % were men. At baseline the patients had a mean duration of diabetes of 5 years and the mean BMI was 32 kg/m^2.

Table 3 SURPASS 1: Results at week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
m-ITT population (n)		121	121	120	113
HbA_{1c} (%)	Baseline (mean)	7.97	7.88	7.88	8.08
	Change from baseline	-1.87##	-1.89##	-2.07##	+0.04
	Difference from placebo [95% CI]	-1.91** [-2.18, -1.63]	-1.93** [-2.21, -1.65]	-2.11** [-2.39, -1.83]	-
Patients (%) achieving HbA_{1c}	<7%	86.8**	91.5**	87.9**	19.6
	≤6.5%	81.8††	81.4††	86.2††	9.8
	<5.7%	33.9**	30.5**	51.7**	0.9
FSG (mmol/L)	Baseline (mean)	8.5	8.5	8.6	8.6
	Change from baseline	-2.4##	-2.6##	-2.7##	+0.7#
	Difference from placebo [95% CI]	-3.13** [-3.71, -2.56]	-3.26** [-3.84, -2.69]	-3.45** [-4.04, -2.86]	-
Body weight (kg)	Baseline (mean)	87.0	85.7	85.9	84.4
	Change from baseline	-7.0##	-7.8##	-9.5##	-0.7
	Difference from placebo [95% CI]	-6.3** [-7.8, -4.7]	-7.1** [-8.6, -5.5]	-8.8** [-10.3, -7.2]	-
Patients (%) achieving weight loss	≥5%	66.9††	78.0††	76.7††	14.3
	≥10%	30.6††	39.8††	47.4††	0.9
	≥15%	13.2†	17.0†	26.7†	0.0

m-ITT - modified intent to treat population (efficacy estimand)
** p < 0.001 for superiority, adjusted for multiplicity.
† p < 0.05, †† p < 0.001 compared to placebo, not adjusted for multiplicity.
# p < 0.05, ## p < 0.001 compared to baseline.

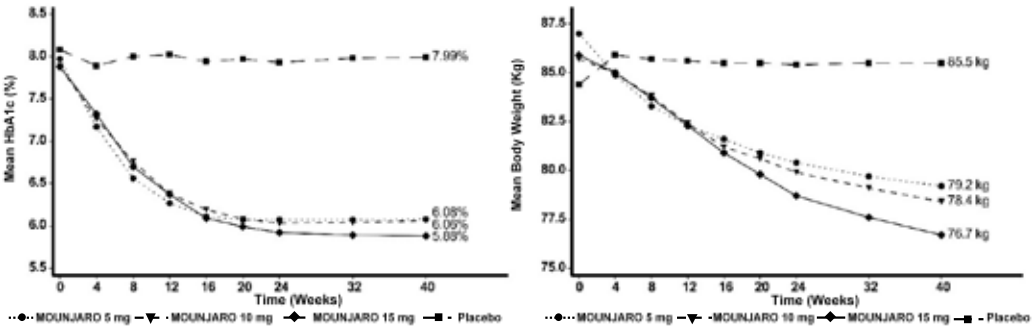


Figure 1 Mean HbA1c (%) from baseline and mean change in body weight (kg) from baseline over time

SURPASS 2 - Combination therapy with metformin

In a 40-week (GPGL) active-controlled open-label study, (double-blind with respect to tirzepatide dose assignment) 1,879 patients were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or semaglutide 1 mg once weekly, all in combination with metformin. Patients had a mean age of 57 years and 47 % were men. At baseline the patients had a mean duration of diabetes of 9 years and the mean BMI was 34 kg/m^2.

Table 4. SURPASS 2: Results at week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 1 mg
m-ITT population (n)		470	469	469	468
HbA_{1c} (%)	Baseline (mean)	8.33	8.31	8.25	8.24
	Change from baseline	-2.09##	-2.37##	-2.46##	-1.86##
	Difference from semaglutide [95% CI]	-0.23** [-0.36, -0.10]	-0.51** [-0.64, -0.38]	-0.60** [-0.73, -0.47]	-
Patients (%) achieving HbA_{1c}	<7%	85.5*	88.9**	92.2**	81.1
	≤6.5%	74.0†	82.1††	87.1††	66.2
	<5.7%	29.3††	44.7**	50.9**	19.7
FSG (mmol/L)	Baseline (mean)	9.67	9.69	9.56	9.49
	Change from baseline	-3.11##	-3.42##	-3.52##	-2.70##
	Difference from semaglutide [95% CI]	- 0.41† [-0.65, -0.16]	- 0.72†† [-0.97, -0.48]	- 0.82†† [-1.06, -0.57]	-
Body weight (kg)	Baseline (mean)	92.6	94.9	93.9	93.8
	Change from baseline	-7.8##	-10.3##	-12.4##	-6.2##
	Difference from semaglutide [95% CI]	-1.7** [-2.6, -0.7]	-4.1** [-5.0, -3.2]	-6.2** [-7.1, -5.3]	-
Patients (% achieving target)	≥5%	68.6†	82.4††	86.2††	58.4
	≥10%	35.8††	52.9††	64.9††	25.3
	≥15%	15.2†	27.7††	39.9††	8.7

m-ITT - modified intent to treat population (efficacy estimand)
* p < 0.05, ** p < 0.001 for superiority, adjusted for multiplicity.
† p < 0.05, †† p < 0.001 compared to semaglutide 1mg, not adjusted for multiplicity.
p < 0.001 compared to baseline.

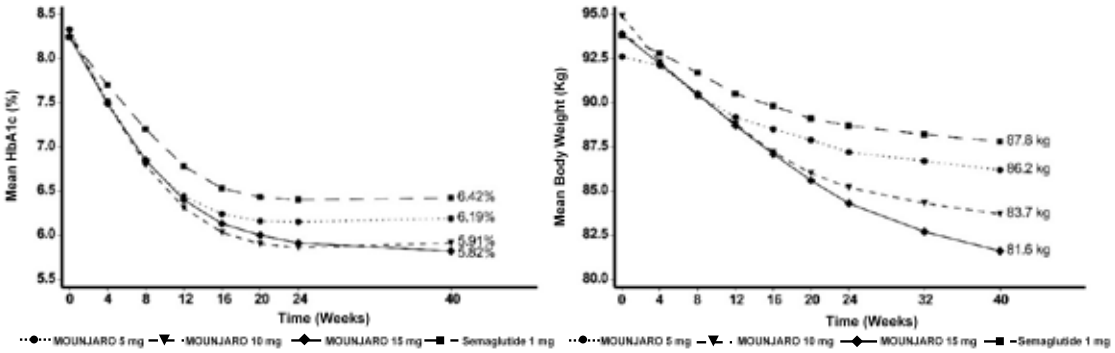


Figure 2 Mean HbA1c (%) from baseline and mean change in body weight (kg) from baseline over time

SURPASS 3 - Combination therapy with metformin, with or without SGLT2i

In a 52-week active-controlled open-label study (GPGH), 1,444 patients were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or insulin degludec, all in combination with metformin and with or without a sodium-glucose co-transporter 2 inhibitor (SGLT2i). 32% of patients were using SGLT2i at baseline. At baseline the patients had a mean duration of diabetes of 8 years, a mean BMI of 34 kg/m^2, a mean age of 57 years and 56 % were men.

Patients treated with insulin degludec started at a dose of 10 U/day which was adjusted using an algorithm for a target fasting blood glucose of < 5 mmol/L. The mean dose of insulin degludec at week 52 was 49 units/day.

Table 5. SURPASS 3: Results at week 52

		Tirzepatide 5 mg	**Tirzepatide 10 mg**	**Tirzepatide 15 mg**	**Titrated insulin degludec[a]**
m-ITT population (n)		358	360	358	359
HbA$_{1c}$ (%)	Baseline (mean)	8.17	8.19	8.21	8.13
	Change from baseline	-1.93##	-2.20##	-2.37##	-1.34##
	Difference from insulin degludec [95% CI]	-0.59** [-0.73, -0.45]	-0.86** [-1.00, 0.72]	-1.04** [-1.17, 0.90]	-
Patients (%) achieving HbA$_{1c}$	<7%	82.4**	89.7**	92.6**	61.3
	≤6.5%	71.4††	80.3††	85.3††	44.4
	<5.7%	25.8††	38.6††	48.4††	5.4
FSG (mmol/L)	Baseline (mean)	9.54	9.48	9.35	9.24
	Change from baseline	-2.68##	-3.04##	-3.29##	-3.09##
	Difference from insulin degludec [95% CI]	0.41† [0.14, 0.69]	0.05 [-0.24, 0.33]	-0.20 [-0.48, 0.08]	-
Body weight (kg)	Baseline (mean)	94.5	94.3	94.9	94.2
	Change from baseline	-7.5##	-10.7##	-12.9##	+2.3##
	Difference from insulin degludec [95% CI]	-9.8** [-10.8, -8.8]	-13.0** [-14.0, -11.9]	-15.2** [-16.2, -14.2]	-
Patients (%) achieving weight loss	≥5%	66.0††	83.7††	87.8††	6.3
	≥10%	37.4††	55.7††	69.4††	2.9
	≥15%	12.5††	28.3††	42.5††	0.0

m-ITT - modified intent to treat population (efficacy estimand)
[a] The mean dose of insulin degludec at week 52 was 49 units/day.
** p < 0.001 for superiority, adjusted for multiplicity.
†† p < 0.001 compared to insulin degludec, not adjusted for multiplicity.
# p < 0.05, ## p < 0.001 compared to baseline.

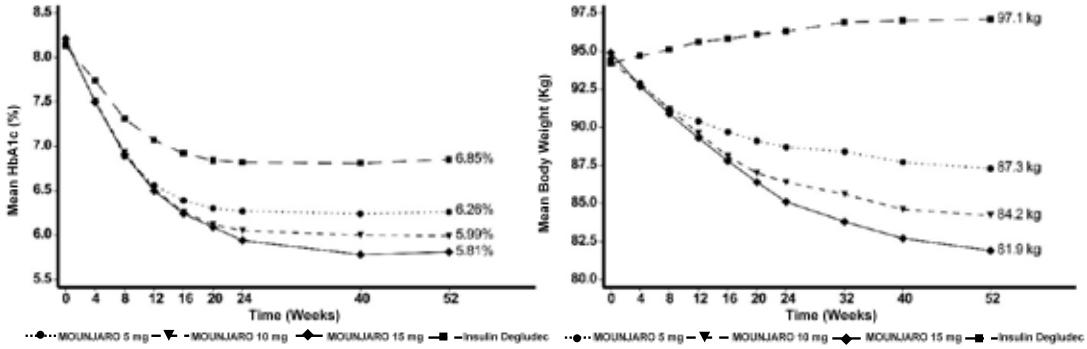


Figure 3 Mean change in HbA1c (%) and body weight (kg) from baseline to week 52

Continuous glucose monitoring (CGM)
A subset of patients (N = 243) participated in an evaluation of the 24-hour glucose profiles captured with blinded CGM. At 52-weeks, patients treated with tirzepatide (10 mg and 15 mg pooled) spent significantly more time with glucose values in the euglycaemic range defined as 3.9 to 7.8 mmol/L compared to patients treated with insulin degludec, with 73% and 48% of the 24-hour period in range, respectively.

At 52-weeks patients in all 3 tirzepatide dose groups spent a greater proportion of the 24-hour period with blood glucose in the range of 3.9 to 10.0 mmol/L than patients treated with insulin degludec: tirzepatide (range), 84.9% to 91.2%; insulin degludec, 75.0%.

Liver fat content (LFC) and adipose tissue

A subset of patients (N = 296) participated in an evaluation of LFC, visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (ASAT) assessed through magnetic resonance imaging. At 52-weeks, patients treated with tirzepatide (10 mg and 15 mg pooled) demonstrated statistically significantly greater mean reductions in LFC compared to insulin degludec, -8.09% versus -3.38% respectively, from baselines of 15.67% and 16.58%. Patients treated with tirzepatide 5 mg, 10 mg and 15 mg had significantly greater reductions in volume of VAT (-1.10, -1.53 and -1.65 L respectively) and ASAT (-1.40, -2.25 and -2.05 L respectively) from overall baselines of 6.6 L and 10.4 L respectively at 52 weeks compared with an increase in the insulin degludec group (0.38 and 0.63 L).

<u>SURPASS 4 – Combination therapy with 1-3 oral antidiabetic medicinal products: metformin, sulfonylureas or SGLT2i</u>

In an active-controlled open-label study of up to 104 weeks (primary endpoint at 52 weeks) (GPGM), 2,002 patients with type 2 diabetes and increased cardiovascular risk were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or insulin glargine once daily on a background of metformin (95%) and/or sulfonylureas (54%) and/or SGLT-2i (25%). At baseline the patients had a mean duration of diabetes of 12 years, a mean BMI of 33 kg/m2, a mean age of 64 years and 63 % were men. Patients treated with insulin glargine started at a dose of 10 U/day which was adjusted using an algorithm with a fasting blood glucose target of < 5.6 mmol/L. The mean dose of insulin glargine at week 52 was 44 units/day.

Table 6. SURPASS 4: Results at week 52

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Titrated insulin glargine[a]
m-ITT population (n)		328	326	337	998
52 weeks					
HbA_{1c} (%)	Baseline (mean)	8.52	8.60	8.52	8.51
	Change from baseline	-2.24##	-2.43##	-2.58##	-1.44##
	Difference from insulin glargine [95% CI]	-0.80** [-0.92, -0.68]	-0.99** [-1.11, -0.87]	-1.14** [-1.26, -1.02]	-
Patients (%) achieving HbA_{1c}	<7%	81.0**	88.2**	90.7**	50.7
	≤6.5%	66.0††	76.0††	81.1††	31.7
	<5.7%	23.0††	32.7††	43.1††	3.4
FSG (mmol/L)	Baseline (mean)	9.57	9.75	9.67	9.37
	Change from baseline	-2.8##	-3.06##	-3.29##	-2.84##
	Difference from insulin glargine [95% CI]	0.04 [-0.22, 0.30]	-0.21 [-0.48, 0.05]	-0.44†† [-0.71, -0.18]	-
Body weight (kg)	Baseline (mean)	90.3	90.7	90.0	90.3
	Change from baseline	-7.1##	-9.5##	-11.7##	+1.9##
	Difference from insulin glargine [95% CI]	-9.0** [-9.8, -8.3]	-11.4** [-12.1, -10.6]	-13.5** [-14.3, -12.8]	-
Patients (%) achieving weight loss	≥5%	62.9††	77.6††	85.3††	8.0
	≥10%	35.9††	53.0††	65.6††	1.5
	≥15%	13.8††	24.0††	36.5††	0.5

m-ITT - modified intent to treat population (efficacy estimand)
[a] The mean dose of insulin glargine at week 52 was 44 units/day.
** $p < 0.001$ for superiority, adjusted for multiplicity.
†† $p < 0.001$ compared to insulin glargine, not adjusted for multiplicity.
$p < 0.001$ compared to baseline.

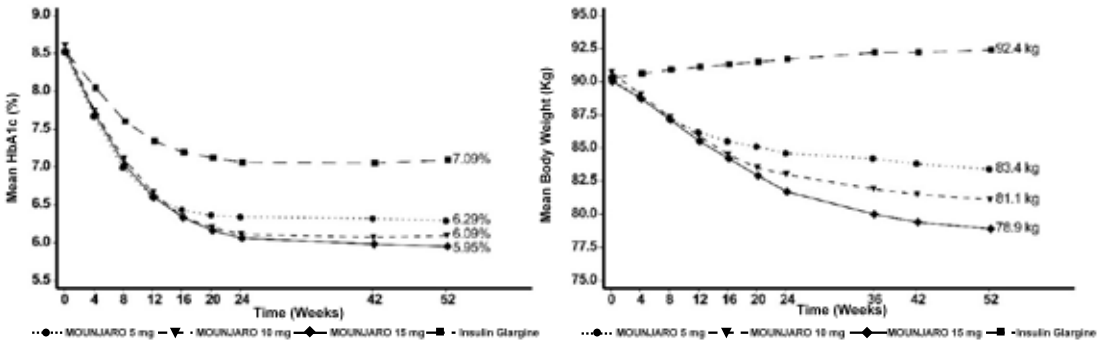


Figure 4 Mean change in HbA1c (%) and body weight (kg) from baseline to week 52

SURPASS 5 - Combination therapy with titrated basal insulin, with or without metformin

In a 40-week double-blind placebo-controlled study (GPGI), 475 patients with inadequate glycaemic control using insulin glargine with or without metformin were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or placebo. Insulin glargine doses were adjusted utilising an algorithm with a fasting blood glucose target of < 5.6 mmol/L. At

baseline the patients had a mean duration of diabetes of 13 years, a mean BMI of 33 kg/m^2, a mean age of 61 years and 56 % were men. The overall estimated median dose of insulin glargine at baseline was 34 units/day. The median dose of insulin glargine at week 40 was 38, 36, 29 and 59 units/day for tirzepatide 5 mg, 10 mg, 15 mg and placebo respectively.

Table 7. SURPASS 5: Results at week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo[a]
m-ITT population (n)		116	118	118	119
HbA_{1c} (%)	Baseline (mean)	8.29	8.34	8.22	8.39
	Change from baseline	-2.23##	-2.59##	-2.59##	-0.93##
	Difference from placebo [95% CI]	-1.30** [-1.52, -1.07]	-1.66** [-1.88, -1.43]	-1.65** [-1.88, -1.43]	-
Patients (%) achieving HbA_{1c}	<7%	93.0**	97.4**	94.0**	33.9
	≤6.5%	80.0††	94.7††	92.3††	17.0
	<5.7%	26.1††	47.8††	62.4††	2.5
FSG (mmol/L)	Baseline (mean)	9.00	9.04	8.91	9.13
	Change from baseline	-3.41##	-3.77##	-3.76##	+2.16##
	Difference from placebo [95% CI]	-1.25** [-1.64, -0.86]	-1.61** [-2.00, -1.22]	-1.60** [-1.99, -1.20]	-
Body weight (kg)	Baseline (mean)	95.5	95.4	96.2	94.1
	Change from baseline	-6.2##	-8.2##	-10.9##	+1.7#
	Difference from placebo [95% CI]	-7.8** [-9.4, -6.3]	-9.9** [-11.5, -8.3]	-12.6** [-14.2, -11.0]	-
Patients (%) achieving weight loss	≥5%	53.9††	64.6††	84.6††	5.9
	≥10%	22.6††	46.9††	51.3††	0.9
	≥15%	7.0†	26.6†	31.6††	0.0

m-ITT - modified intent to treat population (efficacy estimand)

[a] The overall median dose of insulin glargine at baseline was 34 units/day. The median dose of insulin glargine at week 40 was 38, 36, 29 and 59 units/day for tirzepatide 5 mg, 10 mg, 15 mg and placebo respectively.

** $p < 0.001$ for superiority, adjusted for multiplicity.

† $p < 0.05$, †† $p < 0.001$ compared to placebo, not adjusted for multiplicity.

# $p < 0.05$, ## $p < 0.001$ compared to baseline.

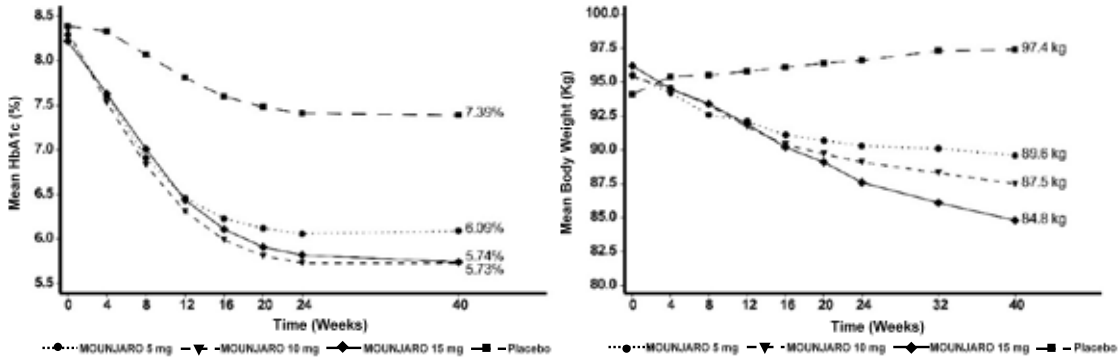


Figure 5 Mean change in HbA1c (%) and body weight (kg) from baseline to week 40

Cardiovascular Evaluation

Cardiovascular (CV) risk was assessed via a meta-analysis of patients with at least one adjudication confirmed major adverse cardiac event (MACE). The composite endpoint of

MACE-4 included CV death, nonfatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina.

In a primary meta-analysis of phase 2 and 3 registration studies, a total of 116 patients (tirzepatide: 60 [n = 4410]; all comparators: 56 [n = 2169]) experienced at least one adjudication confirmed MACE-4: The results showed that tirzepatide was not associated with excess risk for CV events compared with pooled comparators (HR: 0.81; CI: 0.52 to 1.26).

An additional analysis was conducted specifically for the SURPASS-4 study that enrolled patients with established CV disease. A total of 109 patients (tirzepatide: 47 [n=995]; insulin glargine: 62 [n=1000]) experienced at least one adjudication confirmed MACE-4: The results showed that tirzepatide was not associated with excess risk for CV events compared with insulin glargine (HR: 0.74; CI:0.51 to 1.08).

Blood pressure

Treatment with tirzepatide 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.

Other information

Fasting serum glucose

Treatment with tirzepatide resulted in significant reductions from baseline in FSG (changes from baseline to primary end point were -2.4 mmol/L to -3.8 mmol/L). Significant reductions from baseline in FSG could be observed as early as 2 weeks. The improvement in FSG was sustained through the longest study duration of 104 weeks.

Postprandial glucose

Treatment with tirzepatide resulted in significant reductions in mean 2 -hour post prandial glucose (mean of 3 main meals of the day) from baseline (changes from baseline to primary end point were - 3.35 mmol/L to - 4.85 mmol/L).

Pancreatic enzymes

Treatment with tirzepatide resulted in an increase from baseline in pancreatic amylase of 33% to 38% and lipase of 31% to 42%. Placebo-treated patients had an increase from baseline in amylase of 4% and no changes were observed in lipase. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Triglycerides

Across SURPASS 1-5 trials, tirzepatide 5 mg, 10 mg and 15 mg resulted in reduction in serum triglyceride of 15 - 19%, 18 - 27% and 21 - 25% respectively.

In the 40-week trial versus semaglutide 1 mg, tirzepatide 5 mg, 10 mg and 15 mg resulted in 19%, 24% and 25% reduction in serum triglycerides levels respectively compared to 12% reduction with semaglutide 1 mg.

Proportion of patients reaching HbA1c <5.7% without clinically significant hypoglycaemia

In the 4 studies where tirzepatide was not combined with basal insulin, 93.6% to 100% of patients who achieved a normal glycaemia of HbA1c <5.7%, at the primary endpoint visit with tirzepatide treatment did so without clinically significant hypoglycaemia. In Study SURPASS-5, 85.9% patients treated with tirzepatide who reached HbA1c <5.7% did so without clinically significant hypoglycaemia.

Special populations

The efficacy of tirzepatide was not impacted by age, gender, race, ethnicity, region, or by baseline BMI, HbA1c, diabetes duration and level of renal function impairment.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Maximum concentration of tirzepatide is reached 8 to 72 hours post dose. Steady state exposure is achieved following 4 weeks of once weekly administration. Tirzepatide exposure increases in a dose proportional manner. Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm. Absolute bioavailability of subcutaneous tirzepatide was 80%.

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

Excretion

The apparent population mean clearance of tirzepatide is 0.06 L/h with an elimination half-life of approximately 5 days, enabling once weekly administration.

Tirzepatide is eliminated by metabolism. The primary excretion routes of tirzepatide metabolites are via urine and faeces. Intact tirzepatide is not observed in urine or faeces.

Special populations

Age, gender, race, ethnicity, body weight

Age, gender, race, ethnicity or body weight, do not have a clinically relevant effect on the pharmacokinetics (PK) of tirzepatide.

Renal impairment

Renal impairment does not impact the PK of tirzepatide. The PK of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. This was also shown for patients with both type 2 diabetes mellitus and renal impairment based on data from clinical studies.

Hepatic impairment

Hepatic impairment does not impact the PK of tirzepatide. The PK of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function.

Paediatric population

Tirzepatide has not been studied in paediatric patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In an *in vivo* genotoxicity study (bone marrow micronucleus assay) there were no significant increase in micronuclei in polychromatic erythrocytes in bone marrow of male rats after single SC administration of up to 3 mg/kg tirzepatide. Based on the weight of evidence, tirzepatide is not considered genotoxic.

Carcinogenicity

A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.12, 0.36, and 1.02-fold the maximum recommended human dose (MRHD) based on area under the curve (AUC)) administered by subcutaneous injection twice weekly. Tirzepatide caused an increase in thyroid C-cell tumours (adenomas and carcinomas) at all doses compared to controls. The human relevance of these findings is currently unknown.

In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg (up to 11-fold the MRHD based on AUC) administered by subcutaneous injection twice weekly did not produce increased incidences of thyroid C-cell hyperplasia or neoplasia at any dose.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride
Dibasic sodium phosphate heptahydrate
Hydrochloric acid
Sodium hydroxide
Water for Injections

6.2 INCOMPATIBILITIES

Not applicable for subcutaneous single-dose product.

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

MOUNJARO ready-to-use, single-use, pre-filled pens should be stored at 2°C to 8°C, refrigerated. Do not freeze. Do not shake. Store in original carton to protect from light.

In-use

MOUNJARO may be stored unrefrigerated for up to 21 days at temperatures not above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

MOUNJARO is available as a ready-to-use pre-filled pen (autoinjector). The product is contained in a glass syringe (Type 1) encased in a disposable single-dose pen. The syringe has a 29G thin wall ½" staked needle.

MOUNJARO is available in trade packs of 2 or 4 pre-filled pens, and starter packs of 2 pre-filled pens for the 2.5mg/0.5mL presentation.

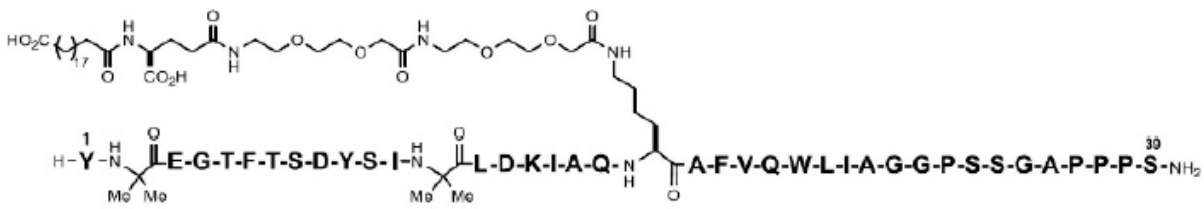
Not all pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Molecular weight:

4,813 Daltons

CAS number

2023788-19-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Medicine

8 SPONSOR

Eli Lilly Australia Pty. Limited

112 Wharf Road, West Ryde, NSW 2114

AUSTRALIA

1800 454 559

9 DATE OF FIRST APPROVAL

23 December 2022

10 DATE OF REVISION

10.1 SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
-	New Product Information

MOUNJARO® is a registered trademark of Eli Lilly and Company