Summary Report of Benefit-Risk Assessment

MOUNJARO INJECTION 2.5MG/0.5ML, 5MG/0.5ML, 7.5MG/0.5ML, 10MG/0.5ML, 12.5MG/0.5ML, 15MG/0.5ML

NEW DRUG APPLICATION

Active Ingredient(s)	Tirzepatide
Product Registrant	DKSH SINGAPORE PTE. LTD.
Product Registration Numbers	SIN16714P, SIN16716P, SIN16717P, SIN16718P, SIN16719P and SIN16720P
Application Route	Full evaluation
Date of Approval	28 February 2023

Table of Contents

A INTRODUCTION

Mounjaro is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus (T2DM).

The active substance, tirzepatide, is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist, which enhances first- and second-phase insulin secretion and reduces glucagon levels.

Mounjaro is available as a solution for injection containing 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 or 15 mg/0.5 mL of tirzepatide. Other ingredients in the pre-filled pen are sodium chloride, sodium phosphate dibasic heptahydrate, hydrochloric acid, sodium hydroxide, and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, tirzepatide, is manufactured at Corden Pharma Colorado, Inc, Colorado, USA. The drug product, Mounjaro Injection, is manufactured at Eli Lilly and Company, Indiana, USA and Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH Q3A, Q3C and Q3D guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the storage of the drug substance at -25°C to -10°C with a re-test period of 24 months. The packaging is LLDPE liner in a laminated foil liner. Each liner is individually cable tied or equivalent. The liners may be placed in an appropriate container such as a corrugated container, fiber drum, polyethylene drum, or metal drum for shipping and handling.

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at 2°C to 8°C. If required, each pre-filled pen can be stored unrefrigerated at temperatures not exceeding 30ºC for up to 21 days. The container closure system is a 1 mL type 1 clear glass syringe barrel with staked needle and elastomeric plunger assembled into a single dose pre-filled pen. Four pre-filled pens are packed inside each carton.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of tirzepatide in the treatment of T2DM was based on 5 pivotal Phase 3 and 2 supportive Phase 3 clinical studies involving approximately 7,342 subjects, as shown in the table below. Studies GPGK (SURPASS-1) and GPGO (SURPASS J-mono) investigated tirzepatide monotherapy, while the other studies investigated combination of tirzepatide with other oral antidiabetic medications or basal insulin.

Overview of the design of the clinical studies

	Pivotal					Supportive	
	GPGK (SURPASS-1)	**GPGL (SURPASS-2)**	**GPGH (SURPASS-3)**	**GPGM (SURPASS-4)**	**GPGI (SURPASS-5)**	**GPGO (SURPASS J-mono)**	**GPGP (SURPASS J-combo)**
Study design	Double-blind	Open-label	Open-label	Open-label	Double-blind	Double-blind	Open-label
TZP doses (weekly)	5, 10, 15 mg						
Comparator	Placebo	Semaglutide 1 mg	Insulin degludec	Insulin glargine	Placebo	Dulaglutide 0.75 mg	None
Randomisation scheme	1:1:1:1			1:1:1:3	1:1:1:1	1:1:1:1	1:1:1
Treatment duration	40 weeks		52 weeks	52 to 104 weeks	40 weeks	52 weeks	52 weeks
No. of patients randomised and treated with study drug	478	1,878	1,437	1,995	475	636	443
No. of patients randomised and treated with TZP	363	1,409	1,077	995	355	477	
Background therapies	None	Metformin	Metformin ± SGLT-2 inhibitor	1 to 3 oral antidiabetics (metformin ± sulfonylurea ± SGLT-2 inhibitor)	Insulin glargine ± metformin	None	1 oral antidiabetic (metformin, sulfonylurea, SGLT-2 inhibitor, α-glucosidase inhibitor, TZD, or glinide)
Primary endpoint	Change from baseline in HbA1c						Safety[a]

TZP = tirzepatide; SGLT-2 inhibitor = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione
[a] SURPASS J-combo was primarily a safety study; efficacy was evaluated as secondary endpoints.

The patients in the pivotal studies were randomised equally into tirzepatide 5 mg, 10 mg or 15 mg and the placebo or active comparator arms, except in study GPGM (SURPASS 4) where the randomisation ratio was 1:1:1:3 to tirzepatide 5 mg, 10 mg, 15 mg, or titrated insulin glargine. The starting dose of tirzepatide was 2.5 mg injected subcutaneously once weekly for 4 weeks and then increased by 2.5 mg every 4 weeks until the maintenance dose of 5 mg, 10 mg or 15 mg once weekly was reached.

The primary efficacy endpoint in the pivotal studies was the mean change from baseline in HbA1c. The key secondary endpoints included the proportion of patients with HbA1c target values of <7.0% and patients with HbA1c target values of <5.7%, as well as the mean change from baseline in fasting serum glucose (FSG) and body weight. The statistical plans were appropriate and the overall type I error was controlled by hierarchical testing.

Across the 5 pivotal studies, a total of 6263 patients were randomly assigned and treated with at least 1 dose of study drug. About 45% of patients were women, 80.4% were White, and 6.8% were Asian. The mean baseline HbA1c ranged from 7.94% to 8.52% (63.3 to 69.7 mmol/mol), the mean age ranged from 54.1 to 63.6 years, the mean BMI ranged from 31.9 to 34.2 kg/m^2, the mean weight ranged from 85.9 to 95.2 kg, and the mean duration of diabetes ranged from 4.7 to 13.3 years.

In study SURPASS 1, tirzepatide 5 mg, 10 mg and 15 mg as monotherapy were superior to placebo in terms of the reduction of HbA1c from baseline at 40 weeks in patients who were managed with only diet and exercise at study entry. The mean treatment differences in HbA1c reduction versus placebo were -1.66% (95% CI: -1.96, -1.36; p<0.001) for tirzepatide 5 mg, -1.62% (95% CI: -1.92, -1.32; p<0.001) for tirzepatide 10 mg and -1.60% (95% CI: -1.91, -1.30; p<0.001) for tirzepatide 15 mg.

In study SURPASS 2, tirzepatide was superior to semaglutide 1 mg in terms of the reduction of HbA1c from baseline at 40 weeks in patients on background metformin. The mean treatment differences in HbA1c reduction versus semaglutide 1 mg were -0.15% (95% CI: -0.28, -0.03; p<0.05) for tirzepatide 5 mg, -0.39% (95% CI: -0.51, -0.26; p<0.001) for tirzepatide 10 mg and -0.45% (95% CI: -0.57, -0.32; p<0.001) for tirzepatide 15 mg.

In study SURPASS 3, tirzepatide was superior to insulin degludec for the reduction of HbA1c from baseline at 52 weeks in patients on background metformin with/without SGLT-2 inhibitors (SGLT-2i). The mean treatment differences in HbA1c reduction versus insulin degludec were -0.60% (95% CI: -0.74, -0.45; p<0.001) for tirzepatide 5 mg, -0.76% (95% CI: -0.90, -0.61; p<0.001) for tirzepatide 10 mg and -0.89% (95% CI: -1.03, -0.74; p<0.001) for tirzepatide 15 mg.

In study SURPASS 4, tirzepatide was superior to insulin glargine for the reduction of HbA1c from baseline at 52 weeks in patients on background of one to three oral antidiabetic medications including metformin, sulphonylureas and/or SGLT-2i. The mean treatment differences in HbA1c reduction versus insulin glargine were -0.72% (95% CI: -0.86, -0.58; p<0.001) for tirzepatide 5 mg, -0.91% (95% CI: -1.05, -0.77; p<0.001) for tirzepatide 10 mg and -1.02% (95% CI: -1.15, -0.89; p<0.001) for tirzepatide 15 mg.

In study SURPASS 5, tirzepatide was superior to placebo for the reduction of HbA1c from baseline at 40 weeks in patients on background of titrated basal insulin, with or without metformin. The mean treatment differences in HbA1c reduction versus placebo were -1.24% (95% CI: -1.48, -1.01; p<0.001) for tirzepatide 5 mg, -1.53% (95% CI: -1.77, -1.30; p<0.001) for tirzepatide 10 mg and -1.47% (95% CI: -1.71, -1.23; p<0.001) for tirzepatide 15 mg.

The positive results in the primary endpoint of reduction of HbA1c from baseline in all the studies were supported by the secondary endpoint results, where tirzepatide demonstrated superiority to placebo or active comparators in terms of the proportion of patients who reached the HbA1c targets of <7.0%, ≤6.5% and <5.7% (p <0.05 in all categories). A dose response was demonstrated as the treatment effects were generally numerically greater with higher doses of tirzepatide. Tirzepatide was also superior to placebo and active comparators in terms of reduction from baseline in FSG (p<0.001). As for body weight loss, more patients achieved body weight loss target of ≥5% in the tirzepatide groups (range: 7% to 86%) compared to the placebo (range: 0% to 14%) and active control groups (range: 0.5% to 58%).

Consistent results were also seen in the supportive Phase 3 studies, SURPASS J-mono and SURPASS J-combo, conducted in Japan. The monotherapy study (SURPASS J-mono) showed superiority of all three doses of tirzapatide (5 mg, 10 mg and 15 mg) to dulaglutide 0.75 mg with regard to change from baseline in HbA1c at 52 weeks (-1.09% (95% CI: -1.27, -0.90) for tirzepatide 5 mg; -1.27% (95% CI -1.45, -1.08) for tirzepatide 10 mg; and -1.53% (95% CI: -1.71, -1.35) for tirzepatide 15 mg. In SURPASS J-combo, which evaluated efficacy as secondary endpoint, consistent decreases from baseline in HbA1c at 52 weeks was observed for all three doses of tirzepatide (-2.6% for tirzepatide 5 mg, -3.0% for tirzepatide 10 mg and -3.0% for tirzepatide 15 mg).

Summary of key efficacy results across the clinical studies

Study	Comparator	Endpoint[a]	Tirzepatide (TZP) dose	Treatment difference (95% CI) / Proportion vs comparator
SURPASS-1 (N=478)	Placebo	Primary: Change from baseline in HbA1C (%)	5 mg	-1.66 (-1.96, -1.36)***
			10 mg	-1.62 (-1.92, -1.32)***
			15 mg	-1.60 (-1.91, -1.30)***
		Secondary: Change from baseline in fasting serum glucose (mg/dL)	5 mg	-43.2 (-54.8, -31.6)***
			10 mg	-43.4 (-55.1, -31.7)***
			15 mg	-42.3 (-54.4, -30.3)***
		Secondary: Change from baseline in body weight (%)	5 mg	-5.3 (-6.8, -3.9)***
			10 mg	-6.0 (-7.4, -4.6)***
			15 mg	-6.8 (-8.3, -5.4)***
		Secondary: Proportion of patients (%) with HbA1c target of <7.0%	5 mg	81.8 vs 23.0***
			10 mg	84.5 vs 23.0***
			15 mg	78.3 vs 23.0***
		Secondary: Proportion of patients (%) with HbA1c target of <5.7%	5 mg	30.9 vs 1.4***
			10 mg	26.8 vs 1.4***
			15 mg	38.4 vs 1.4***
SURPASS-2 (N=1,878)	Semaglutide	Primary: Change from baseline in HbA1C (%)	5 mg	-0.15 (-0.28, -0.03)*
			10 mg	-0.39 (-0.51, -0.26)***
			15 mg	-0.45 (-0.57, -0.32)***
		Secondary: Change from baseline in fasting serum glucose (mg/dL)	5 mg	-5.4 (-9.7, -1.1)[#]
			10 mg	-9.7 (-14.1, -5.2)[###]
			15 mg	-10.8 (-15.1, -6.5)[###]

		Secondary: Change from baseline in body weight (%)	5 mg	-1.9 (-2.8, -1.0)***
			10 mg	-3.6 (-4.5, -2.7)***
			15 mg	-5.5 (-6.4, -4.6)***
		Secondary: Proportion of patients (%) with HbA1c target of <7.0%	5 mg	82.0 vs 79.0
			10 mg	85.6 vs 79.0**
			15 mg	86.2 vs 79.0**
		Secondary: Proportion of patients (%) with HbA1c target of <5.7%	5 mg	27.1 vs 18.9###
			10 mg	39.8 vs 18.9***
			15 mg	45.7 vs 18.9***
SURPASS-3 (N=1,437)	Insulin degludec	Primary: Change from baseline in HbA1C (%)	5 mg	-0.60 (-0.74, -0.45)***
			10 mg	-0.76 (-0.90, -0.61)***
			15 mg	-0.89 (-1.03, -0.74)***
		Secondary: Change from baseline in fasting serum glucose (mg/dL)	5 mg	3.5 (-2.8, 9.7)
			10 mg	0.3 (-6.0, 6.6)
			15 mg	-3.8 (-9.9, 2.4)
		Secondary: Change from baseline in body weight (%)	5 mg	-8.9 (-10.0, -7.8)***
			10 mg	-11.5 (-12.6, -10.4)***
			15 mg	-13.2 (-14.3, -12.1)***
		Secondary: Proportion of patients (%) with HbA1c target of <7.0%	5 mg	79.2 vs 58.0***
			10 mg	81.5 vs 58.0***
			15 mg	83.5 vs 58.0***
		Secondary: Proportion of patients (%) with HbA1c target of <5.7%	5 mg	23.6 vs 5.1###
			10 mg	33.9 vs 5.1###
			15 mg	40.7 vs 5.1###
SURPASS-4 (N=1,995)	Insulin glargine	Primary: Change from baseline in HbA1C (%)	5 mg	-0.72 (-0.86, -0.58)***
			10 mg	-0.91 (-1.05, -0.77)***
			15 mg	-1.02 (-1.15, -0.89)***
		Secondary: Change from baseline in fasting serum glucose (mg/dL)	5 mg	4.5 (-1.7, 10.8)
			10 mg	-1.5 (-7.3, 4.3)
			15 mg	-5.7 (-11.3, -0.1)#
		Secondary: Change from baseline in body weight (%)	5 mg	-8.1 (-8.9, -7.3)***
			10 mg	-10.6 (-11.4, -9.8)***
			15 mg	-12.2 (-13.0, -11.5)***
		Secondary: Proportion of patients (%) with HbA1c target of <7.0%	5 mg	75.1 vs 48.8***
			10 mg	82.9 vs 48.8***
			15 mg	84.9 vs 48.8***
		Secondary: Proportion of patients (%) with HbA1c target of <5.7%	5 mg	21.7 vs 3.5###
			10 mg	31.1 vs 3.5###
			15 mg	38.0 vs 3.5###
SURPASS-5 (N=475)	Placebo	Primary: Change from baseline in HbA1C (%)	5 mg	-1.24 (-1.48, -1.01)***
			10 mg	-1.53 (-1.77, -1.30)***
			15 mg	-1.47 (-1.71, -1.23)***

		Secondary: Change from baseline in fasting serum glucose (mg/dL)	5 mg	-19.0 (-26.6, -11.4)***
			10 mg	-24.9 (-32.3, -17.4)***
			15 mg	-23.4 (-31.0, -15.8)***
		Secondary: Change from baseline in body weight (%)	5 mg	-7.1 (-8.7, -5.4)***
			10 mg	-9.1 (-10.7, -7.5)***
			15 mg	-10.5 (-12.1, -8.8)***
		Secondary: Proportion of patients (%) with HbA1c target of <7.0%	5 mg	87.3 vs 34.5***
			10 mg	89.6 vs 34.5***
			15 mg	84.7 vs 34.5***
		Secondary: Proportion of patients (%) with HbA1c target of <5.7%	5 mg	24.4 vs 2.7###
			10 mg	41.6 vs 2.7***
			15 mg	49.6 vs 2.7***
SURPASS J-mono (N=477)	Dulaglutide	Primary: Change from baseline in HbA1C (%)	5 mg	-1.09 (-1.27, -0.90)***
			10 mg	-1.27 (-1.45, -1.08)***
			15 mg	-1.53 (-1.71, -1.35)***
		Secondary: Change from baseline in body weight (%)	5 mg	-5.2 (-6.4, - 4.1)***
			10 mg	-7.9 (-9.1, -6.8)***
			15 mg	-10.1 (-11.3, -9.0)***

[a]Efficacy endpoints were evaluated at Week 40 for SURPASS-1, SURPASS-2, and SURPASS-5, and at Week 52 for SURPASS-3, SURPASS-4, and SURPASS J-mono.
*p<0.05, **p<0.01, ***p<0.001 vs comparator, subject to type 1 error control.
#Nominal p<0.05, ##Nominal p<0.01, ###Nominal p<0.001 vs comparator.

Overall, the efficacy of tirzepatide had been adequately demonstrated in terms of robust and clinically meaningful reductions in HbA1c, fasting serum glucose and body weight, which were superior to placebo and active comparators such as semaglutide, insulin degludec, and insulin glargine.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of tirzepatide was based primarily on safety data from the placebo-controlled Phase 3 studies (SURPASS-1 and SURPASS-5), comprising 718 patients treated with tirzepatide (237 patients in the 5 mg group, 240 patients in the 10 mg group and 241 patients in the 15 mg group) and 235 patients who received placebo. In addition, safety data was pooled from all 7 Phase 3 studies (SURPASS-1, SURPASS-2, SURPASS-3, SURPASS-4, SURPASS-5, SURPASS J-mono and SURPASS J-combo), comprising a total of 5,119 patients on tirzepatide (1,701 patients in the 5 mg group, 1,702 patients in the 10 mg group and 1,716 patients in the 15 mg group). The treatment duration across all the studies ranged from 40 to 104 weeks.

Overview of adverse events (AEs) from the placebo-controlled studies

AE	TZP 5 mg (N=237)	TZP 10 mg (N=240)	TZP 15 mg (N=241)	TZP (Pooled) (N=718)	Placebo (N=235)
Any AE	168 (70.9%)	162 (67.5%)	171 (71.0%)	501 (69.8%)	157 (66.8%)
SAE	14 (5.9%)	15 (6.3%)	10 (4.1%)	39 (5.4%)	13 (5.5%)
Discontinuation from study drug due to AE	11 (4.6%)	16 (6.7%)	21 (8.7%)	48 (6.7%)	6 (2.6%)

Deaths due to AE	0	0	0	0	1 (0.4%)

Overview of AEs from the pooled Phase 3 studies

AE	TZP 5 mg (N=1,701)	TZP 10 mg (N=1,702)	TZP 15 mg (N=1,716)	TZP (Pooled) (N=5,119)
Any AE	1,158 (68.08%)	1,202 (70.62%)	1,276 (74.36%)	3,636 (71.03%)
SAE	134 (7.88%)	135 (7.93%)	122 (7.11%)	391 (7.64%)
Discontinuation from study drug due to AE	121 (7.11%)	145 (8.52%)	169 (9.85%)	435 (8.50%)
Deaths due to AE	20 (1.18%)	8 (0.47%)	13 (0.76%)	41 (0.80%)

The overall incidence of AEs in the placebo-controlled studies was similar between the tirzepatide group (69.8%) and the placebo group (66.8%). The common AEs reported with tirzepatide, such as nausea (tirzepatide vs placebo: 15.3% vs 4.3%), diarrhoea (13.8% vs 8.9%), decreased appetite (8.8% vs 1.3%), dyspepsia (7.0% vs 2.6%), vomiting (6.4% vs 2.1%) and constipation (6.1% vs 1.3%), were generally in line with the known safety profile of GLP-1 receptor agonists. Across the 7 Phase 3 studies, the AEs that showed incremental increase with higher dose groups were nausea (13.17% for tirzepatide 5 mg vs 18.33% for tirzepatide 10 mg vs 22.20% for tirzepatide 15 mg), decreased appetite (7.76% vs 9.75% vs 11.66%) and vomiting (5.47% vs 7.76% vs 9.73%).

In the placebo-controlled studies, the overall incidence of serious AEs (SAEs) was similar between the tirzepatide group (5.4%) and the placebo group (5.5%). The SAEs reported were mainly from the cardiac disorders (1.3% in tirzepatide group vs 1.7% in placebo group), infections and infestation (1.1% vs 0.4%), and respiratory disorders (0.7% vs 0.4%) system organ class (SOC). There was no specific trend observed and the incidences were low (one to three cases each) across the SAEs reported. The proportions of patients reporting SAEs were similar across the 3 tirzepatide dose groups (7.88% for tirzepatide 5 mg vs 7.93% for tirzepatide 10 mg vs 7.11% for tirzepatide 15 mg) in the pooled Phase 3 studies. The rate of clinically significant hypoglycaemia (<3.0 mmol/L) was also observed to be low and ranged 0.01 to 0.24 events per year.

The incidence of discontinuations due to AEs in the placebo-controlled trials were higher in the tirezepatide group (6.7%) than in the placebo group (2.6%). Overall, the proportions of patients who discontinued tirzepatide due to an AE ranged from 5.0% to 9.4% across the Phase 3 studies. The most common reasons among tirzepatide-treated patients were gastrointestinal related, including nausea, diarrhoea, gastrointestinal disorder, vomiting, and dyspepsia. This was not unexpected given that tirzepatide exerted its function by binding to the GIP and GLP-1 receptors and gastrointestinal AEs are known AEs of the GLP-1 receptor agonist class of drugs.

The overall incidence of death due to AEs in the placebo-controlled studies was low: none in the tirzepatide group and 1 death in the placebo group. Across all the Phase 2/3 studies, 41 deaths (exposure adjusted, 0.76 per 100 patient-years) occurred in patients treated with tirzepatide compared with 39 deaths (exposure adjusted, 0.86 per 100 patient-years) for the pooled comparators. The estimated HR for all-cause death was 0.80 (95% CI: 0.51, 1.25). The most common causes of death were cardiovascular events, primary sudden cardiac death (N=20), and infections, which included infections related to COVID-19 (N=20).

The AEs of special interest reported with tirzepatide included hypoglycaemia, gastrointestinal AEs, renal and dehydration AEs, pancreatitis, diabetic retinopathy and injection site reactions.

These AEs are known to be associated with GLP-1 receptor agonists and have been adequately described in the package insert.

Cardiovascular (CV) safety was assessed in a meta-analysis comprising all placebo- or active-controlled Phase 2/3 studies with a treatment period lasting 26 weeks or longer. The meta-analysis included 7,215 patients (4,887 patients in the tirzepatide group and 2,328 patients in the pooled comparators group) with a broad spectrum with regard to the disease stages, background antidiabetic medications, and renal impairment status. The primary endpoint was a 4-point major adverse CV event (MACE) composite endpoint, comprising adjudicated events of CV death, myocardial infarction, stroke, and hospitalisation for unstable angina. The final analysis was performed after accrual of 142 primary endpoint events. The results showed that the hazard ratio (HR) for the primary endpoint was 0.80 (95% CI: 0.57, 1.11). To further characterise the CV safety, the sponsor had initiated a Phase 3 Study GPGN (SURPASS-CVOT), which is a long-term, double-blind, active comparator-controlled CV outcomes study to assess the superiority of tirzepatide (up to 15 mg) compared with dulaglutide (1.5 mg) for the reduction of MACE in adult patients with T2DM. The registrant is required to submit the results from this study to confirm the long-term CV safety of tirzepatide as a registration condition.

Overall, the safety profile of tirzepatide in T2DM was considered to be clinically manageable and no major safety concerns were observed. The safety profile of tirzepatide was also similar to that of other GLP-1 receptor agonists currently approved for the treatment of T2DM.

E ASSESSMENT OF BENEFIT-RISK PROFILE

T2DM is a progressive disease typically requiring stepwise intensification of pharmacotherapy. Several classes of antihyperglycaemic agents are currently available for the pharmacological treatment of T2DM. These agents may be used as monotherapy or as part of a variety of combinations. Novel medications offering glucose-lowering efficacy combined with benefits on body weight control could provide more alternatives to patients.

The clinical efficacy of Mounjaro for the treatment of adults with T2DM as an adjunct to diet and exercise as monotherapy, or in addition to other medicinal products for the treatment of T2DM, was supported by five pivotal Phase 3 clinical studies which investigated the effects of tirzepatide 5 mg, 10 mg and 15 mg doses on the lowering of HbA1c and body weight. The results showed that all three tirzepatide doses as monotherapy or in combination with metformin, other oral antihyperglycemic agents or insulin was superior to placebo or active comparators such as semaglutide 1 mg, insulin degludec and insulin glargine for the reduction of HbA1c from baseline. A dose response was observed as the treatment effect was numerically greater with increased doses of tirzepatide.

The positive results in the primary endpoint of reduction of HbA1c from baseline in all the studies were also supported by the secondary endpoint results where tirzepatide consistently demonstrated superiority to placebo in terms of the proportion of patients who achieved HbA1c target of <7.0%. Tirzepatide was also superior to placebo in reduction from baseline in fasting serum glucose. More patients in the tirzepatide group achieved weight loss target of ≥5% compared to the patients in the placebo or active comparator groups.

Tirzepatide was generally well tolerated. Gastrointestinal AEs such as nausea, diarrhoea and decreased appetite were the most common AEs. The overall incidence of SAEs and severe

hypoglycaemia attributable to tirzepatide was also low. The safety profile of tirzepatide was clinically manageable and consistent with what is known for the GLP-1 receptor agonist class of drugs.

Overall, the benefit-risk profile of Mounjaro for use as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM was favourable as efficacy and safety had been demonstrated.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Mounjaro as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus was deemed favourable and approval of the product registrations were granted on 28 February 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

USPI13MAY2022
Mounjaro™ (tirzepatide) Injection, for subcutaneous use

WARNING: RISK OF THYROID C-CELL TUMORS

- **In both male and female rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **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) *[see Contraindications (4)]*. 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). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with MOUNJARO *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

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

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

- The recommended starting dosage of MOUNJARO is 2.5 mg injected subcutaneously once weekly. The 2.5 mg dosage is for treatment initiation and is not intended for glycemic control.
- After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly.
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The maximum dosage of MOUNJARO is 15 mg injected subcutaneously once weekly.
- If a dose is missed, instruct patients to administer MOUNJARO 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.
- The day of weekly administration can be changed, if necessary, as long as the time between the two doses is at least 3 days (72 hours).

2.2 Important Administration Instructions

- Administer MOUNJARO once weekly, any time of day, with or without meals.
- Inject MOUNJARO subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.
- Inspect MOUNJARO visually before use. It should appear clear and colorless 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.
- In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

3 DOSAGE FORMS AND STRENGTHS

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

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

Not all strengths, pack sizes or presentations may be marketed.

4 CONTRAINDICATIONS

MOUNJARO is contraindicated in patients with:

- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Warnings and Precautions (5.1)]*.
- Known serious hypersensitivity to tirzepatide or any of the excipients in MOUNJARO *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors

In both sexes of rats, tirzepatide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) in a 2-year study at clinically relevant plasma exposures *[see Nonclinical Toxicology (13.1)]*. It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined.

MOUNJARO is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of MOUNJARO and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with MOUNJARO. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin values may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists.

In clinical studies, 14 events of acute pancreatitis were confirmed by adjudication in 13 MOUNJARO-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 comparator-treated patients (0.11 patients per 100 years of exposure). MOUNJARO has not been studied in patients with a prior history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on MOUNJARO.

After initiation of MOUNJARO, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue MOUNJARO and initiate appropriate management.

5.3 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients receiving MOUNJARO in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia *[see Adverse Reactions (6.1), Drug Interactions (7.1)]*.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

5.4 Hypersensitivity Reactions

Hypersensitivity reactions have been reported with MOUNJARO in clinical trials (e.g., urticaria and eczema) and were sometimes severe. 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 serious hypersensitivity reaction to tirzepatide or any of the excipients in MOUNJARO *[see Contraindications (4)]*.

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

5.5 Acute Kidney Injury

MOUNJARO has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhea *[see Adverse Reactions (6.1)]*. These events may lead to dehydration, which if severe could cause acute kidney injury.

In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of MOUNJARO in patients with renal impairment reporting severe gastrointestinal adverse reactions.

5.6 Severe Gastrointestinal Disease

Use of MOUNJARO has been associated with gastrointestinal adverse reactions, sometimes severe *[see Adverse Reactions 6.1]*. MOUNJARO has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

5.7 Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy

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

5.8 Acute Gallbladder Disease

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

In MOUNJARO placebo-controlled clinical trials, acute gallbladder disease (cholelithiasis, 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin *[see Warnings and Precautions (5.3)]*
- Hypersensitivity *[see Warnings and Precautions (5.4)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.5)]*
- Severe Gastrointestinal Disease *[see Warnings and Precautions (5.6)]*
- Diabetic Retinopathy Complications *[see Warnings and Precautions (5.7)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pool of Two Placebo-Controlled Clinical Trials

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

Pool of Seven Controlled Clinical Trials

Adverse reactions were also evaluated in a larger pool of adult patients with type 2 diabetes mellitus participating in seven controlled clinical trials which included two placebo-controlled trials (SURPASS-1 and -5), three trials of MOUNJARO in combination with metformin, sulfonylureas, and/or SGLT2 Inhibitors (SURPASS-2, -3, -4) *[see Clinical Studies (14.3)]* and two additional trials conducted in Japan. In this pool, a total of 5119 adult patients with type 2 diabetes mellitus were treated with MOUNJARO for a mean duration of 48.1 weeks. The mean age of patients was 58 years, 4% were 75 years or older and 58% were male. The population was 65% White, 24% Asian, 7% American Indian or Alaska Native, and 3% Black or African American; 38% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes mellitus for an average of 9.1 years with a mean HbA1c of 8.3%. As assessed by baseline fundoscopic examination, 15% of the population had retinopathy. At baseline, eGFR was ≥90 mL/min/1.73 m^2 in 52%, 60 to 90 mL/min/1.73 m^2 in 40%, 45 to 60 mL/min/1.73 m^2 in 6%, and 30 to 45 mL/min/1.73 m^2 in 1% of patients.

Common Adverse Reactions

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

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

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

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

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

Gastrointestinal Adverse Reactions

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

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

Other Adverse Reactions

Hypoglycemia

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

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

	Placebo %	MOUNJARO 5 mg %	MOUNJARO 10 mg %	MOUNJARO 15 mg %
Monotherapy				
(40 weeks)*	N=115	N=121	N=119	N=120
Blood glucose <54 mg/dL	1	0	0	0
Severe hypoglycemia**	0	0	0	0
Add-on to Basal Insulin with or without Metformin				
(40 weeks)*	N=120	N=116	N=119	N=120
Blood glucose <54 mg/dL	13	16	19	14
Severe hypoglycemia**	0	0	2	1

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

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

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

Heart Rate Increase

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

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with MOUNJARO in the pool of placebo-controlled trials, sometimes severe (e.g., urticaria and eczema); 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 Clinical Pharmacology (12.6)]*.

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 *[see Clinical Pharmacology (12.6)]*.

Acute Gallbladder Disease

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

Laboratory Abnormalities

Amylase and Lipase Increase

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

7 DRUG INTERACTIONS

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

When initiating MOUNJARO, consider reducing the dose of concomitantly administered insulin secretagogues (e.g., sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.3)]*.

7.2 Oral Medications

MOUNJARO delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with MOUNJARO.

Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with MOUNJARO.

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. Hormonal contraceptives that are not administered orally should not be affected *[see Use in Specific Populations (8.3) and Clinical Pharmacology (12.2, 12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with MOUNJARO use in pregnant women are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. MOUNJARO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered tirzepatide during organogenesis, fetal growth reductions and fetal abnormalities occurred at clinical exposure in maternal rats based on AUC. In rabbits administered tirzepatide during organogenesis, fetal growth reductions were observed at clinically relevant exposures based on AUC. These adverse embryo/fetal effects in animals coincided with pharmacological effects on maternal weight and food consumption *(see Data)*.

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA1c >7% and has been reported to be as high as 20–25% in women with an HbA1c >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

Data

Animal Data

In pregnant rats given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide (0.03-, 0.07-, and 0.5-fold the MRHD of 15 mg once weekly based on AUC) during organogenesis, increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and decreased fetal weights coincided with pharmacologically-mediated reductions in maternal body weights and food consumption at 0.5 mg/kg. In pregnant rabbits given once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg tirzepatide (0.01-, 0.06-, and 0.2-fold the MRHD) during organogenesis, pharmacologically-mediated effects on the gastrointestinal system resulting in maternal mortality or abortion in a few rabbits occurred at all dose levels. Reduced fetal weights associated with decreased maternal food consumption and body weights were observed at 0.1 mg/kg. In a pre- and post-natal study in rats administered subcutaneous doses of 0.02, 0.10, or 0.25 mg/kg tirzepatide twice weekly from implantation through lactation, F_1 pups from F_0 maternal rats given 0.25 mg/kg tirzepatide had statistically significant lower mean body weight when compared to controls from post-natal day 7 through post-natal day 126 for males and post-natal day 56 for females.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

Use of MOUNJARO may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying. This delay is largest after the first dose and diminishes over time. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO *[see Drug Interactions (7.2) and Clinical Pharmacology (12.2, 12.3)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the pool of seven clinical trials, 1539 (30.1%) 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.

8.6 Renal Impairment

No dosage adjustment of MOUNJARO is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no change in tirzepatide pharmacokinetics (PK) was observed *[see Clinical Pharmacology (12.3)]*. Monitor renal function when initiating or escalating doses of MOUNJARO in patients with renal impairment reporting severe adverse gastrointestinal reactions *[see Warnings and Precautions (5.5)]*.

8.7 Hepatic Impairment

No dosage adjustment of MOUNJARO is recommended for patients with hepatic impairment. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no change in tirzepatide PK was observed *[see Clinical Pharmacology (12.3)]*.

9.0 Effects on the Ability to Drive and Use Machines

No studies on the effects of 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 hypoglycemia while driving and using machines.

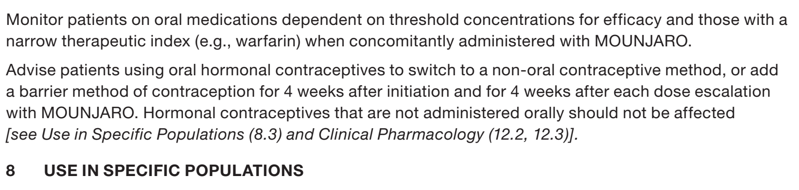
10 OVERDOSAGE

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

11 DESCRIPTION

MOUNJARO (tirzepatide) injection, for subcutaneous use, contains tirzepatide, a once weekly GIP receptor and GLP-1 receptor agonist. It is a 39-amino-acid modified peptide based on the GIP sequence. Tirzepatide contains 2 non-coded amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 that is attached to 1,20-eicosanedioic acid via a linker. The molecular weight is 4813.53 Da and the empirical formula is $C_{225}H_{348}N_{48}O_{68}$.

Structural formula:



MOUNJARO is a clear, colorless to slightly yellow, sterile, preservative-free solution for subcutaneous use. Each single-dose pen contains a 0.5 mL solution of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg of tirzepatide and the following excipients: sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 – 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It is a 39-amino-acid modified peptide with a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.

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

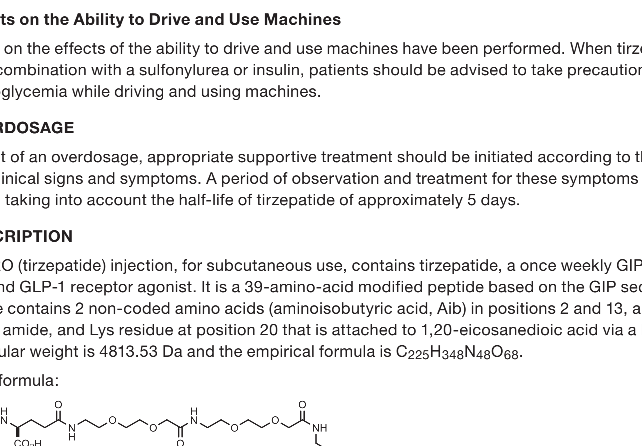
12.2 Pharmacodynamics

Tirzepatide lowers fasting and postprandial glucose concentration, decreases food intake, and reduces body weight in patients with type 2 diabetes mellitus.

First and Second-Phase Insulin Secretion

Tirzepatide enhances the first- and second-phase insulin secretion. (Figure 1)

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



Insulin Sensitivity

Tirzepatide increases insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study after 28 weeks of treatment.

Glucagon Secretion

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

Gastric Emptying

Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time. Tirzepatide slows post-meal glucose absorption, reducing postprandial glucose.

12.3 Pharmacokinetics

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with type 2 diabetes mellitus. Steady-state plasma tirzepatide concentrations were achieved following 4 weeks of once weekly administration. Tirzepatide exposure increases in a dose-proportional manner.

Absorption

Following subcutaneous administration, the time to maximum plasma concentration of tirzepatide ranges from 8 to 72 hours. The mean absolute bioavailability of tirzepatide following subcutaneous administration is 80%. Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm.

Distribution

The mean apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with type 2 diabetes mellitus is approximately 10.3 L. Tirzepatide is highly bound to plasma albumin (99%).

Elimination

The apparent population mean clearance of tirzepatide is 0.061 L/h with an elimination half-life of approximately 5 days, enabling once-weekly dosing.

Metabolism

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

Excretion

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

Specific Populations

The intrinsic factors of age, gender, race, ethnicity, or body weight do not have a clinically relevant effect on the PK of tirzepatide.

Patients with Renal Impairment

Renal impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. This was also shown for patients with both type 2 diabetes mellitus and renal impairment based on data from clinical studies *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

Hepatic impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function *[see Use in Specific Populations (8.7)]*.

Drug Interactions Studies

Potential for Tirzepatide to Influence the Pharmacokinetics of Other Drugs

In vitro studies have shown low potential for tirzepatide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

MOUNJARO delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications *[see Drug Interactions (7.2)]*.

The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses.

Following a first dose of tirzepatide 5 mg, acetaminophen maximum concentration (C_{max}) was reduced by 50%, and the median peak plasma concentration (t_{max}) occurred 1 hour later. After coadministration at week 4, there was no meaningful impact on acetaminophen C_{max} and t_{max}. Overall acetaminophen exposure ($AUC_{0\text{-}24hr}$) was not influenced.

Following administration of a combined oral contraceptive (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single dose of tirzepatide 5 mg, mean C_{max} of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%,66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in t_{max} of 2.5 to 4.5 hours was observed.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the trials described below with the incidence of anti-drug antibodies in other trials, including those of tirzepatide or of GLP-1 receptor agonist products.

During the 40- to 104-week treatment periods with ADA sampling conducted up to 44 to 108 weeks in seven clinical trials in adults with type 2 diabetes mellitus *[see Clinical Studies (14)]*, 51% (2,570/5,025) of MOUNJARO-treated patients developed anti-tirzepatide antibodies. In these trials, anti-tirzepatide antibody formation in 34% and 14% of MOUNJARO-treated patients showed cross-reactivity to native GIP or native GLP-1, respectively.

Of the 2,570 MOUNJARO-treated patients who developed anti-tirzepatide antibodies during the treatment periods in these seven trials, 2% and 2% developed neutralizing antibodies against tirzepatide activity on the GIP or GLP-1 receptors, respectively, and 0.9% and 0.4% developed neutralizing antibodies against native GIP or GLP-1, respectively.

There was no identified clinically significant effect of anti-tirzepatide antibodies on pharmacokinetics or effectiveness of MOUNJARO. More MOUNJARO-treated patients who developed anti-tirzepatide antibodies experienced hypersensitivity reactions or injection site reactions than those who did not develop these antibodies *[see Adverse Reactions (6.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.1-, 0.4-, and 1-fold the MRHD of 15 mg once weekly based on AUC) administered by subcutaneous injection twice weekly. A statistically significant increase in thyroid C-cell adenomas was observed in males (≥0.5 mg/kg) and females (≥0.15 mg/kg), and a statistically significant increase in thyroid C-cell adenomas and carcinomas combined was observed in males and females at all doses examined. In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered by subcutaneous injection twice weekly was not tumorigenic.

Tirzepatide was not genotoxic in a rat bone marrow micronucleus assay.

In fertility and early embryonic development studies, male and female rats were administered twice weekly subcutaneous doses of 0.5, 1.5, or 3 mg/kg (0.3-, 1-, and 2-fold and 0.3-, 0.9-, and 2-fold, respectively, the MRHD of 15 mg once weekly based on AUC). No effects of tirzepatide were observed on sperm morphology, mating, fertility, and conception. In female rats, an increase in the number of females with prolonged diestrus and a decrease in the mean number of corpora lutea resulting in a decrease in the mean number of implantation sites and viable embryos was observed at all dose levels. These effects were considered secondary to the pharmacological effects of tirzepatide on food consumption and body weight.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The effectiveness of MOUNJARO as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus was established in five trials. In these trials, MOUNJARO was studied as monotherapy (SURPASS-1); as an add-on to metformin, sulfonylureas, and/or sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) (SURPASS-2, -3, and -4); and in combination with basal insulin with or without metformin (SURPASS-5). In these trials, MOUNJARO (5 mg, 10 mg, and 15 mg given subcutaneously once weekly) was compared with placebo, semaglutide 1 mg, insulin degludec, and/or insulin glargine.

In adult patients with type 2 diabetes mellitus, treatment with MOUNJARO produced a statistically significant reduction from baseline in HbA1c compared to placebo. The effectiveness of MOUNJARO was not impacted by age, gender, race, ethnicity, region, or by baseline BMI, HbA1c, diabetes duration, or renal function.

14.2 Monotherapy Use of MOUNJARO in Adult Patients with Type 2 Diabetes Mellitus

SURPASS-1 (NCT03954834) was a 40-week double-blind trial that randomized 478 adult patients with type 2 diabetes mellitus with inadequate glycemic control with diet and exercise to MOUNJARO 5 mg, MOUNJARO 10 mg, MOUNJARO 15 mg, or placebo once weekly.

Patients had a mean age of 54 years, and 52% were men. The mean duration of type 2 diabetes mellitus was 4.7 years, and the mean BMI was 32 kg/m^2. Overall, 36% were White, 35% were Asian, 25% were American Indians/Alaska Natives, and 5% were Black or African American; 43% identified as Hispanic or Latino ethnicity.

Monotherapy with 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 3).

Table 3: 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

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

[a] The modified intent-to-treat population consists of all randomly assigned participants who were exposed to at least 1 dose of study drug. Patients who discontinued study treatment because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 25%, 2%, 3%, and 2% of patients randomized to placebo, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. At Week 40 the HbA1c data were missing for 12%, 6%, 7%, and 14% of patients randomized to placebo, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. Missing Week 40 data were imputed using placebo-based multiple imputation.

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

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

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

14.3 MOUNJARO Use in Combination with Metformin, Sulfonylureas, and/or SGLT2 Inhibitors in Adult Patients with Type 2 Diabetes Mellitus

Add-on to metformin

SURPASS-2 (NCT03987919) was a 40-week open-label trial (double-blind with respect to MOUNJARO dose assignment) that randomized 1879 adult patients with type 2 diabetes mellitus with inadequate glycemic control on stable doses of metformin alone to the addition of MOUNJARO 5 mg, MOUNJARO 10 mg, or MOUNJARO 15 mg once weekly or subcutaneous semaglutide 1 mg once weekly.

Patients had a mean age of 57 years and 47% were men. The mean duration of type 2 diabetes mellitus was 8.6 years, and the mean BMI was 34 kg/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 4 and Figure 2).

Table 4: Results at Week 40 in a Trial of MOUNJARO versus Semaglutide 1 mg in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin

	Semaglutide 1 mg	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	468	470	469	469
HbA1c (%)				
Baseline (mean)	8.3	8.3	8.3	8.3
Change at Week 40[b]	-1.9	-2.0	-2.2	-2.3
Difference from semaglutide[b] (95% CI)	--	-0.2[c] (-0.3, -0.0)	-0.4[d] (-0.5, -0.3)	-0.5[d] (-0.6, -0.3)
Patients (%) achieving HbA1c <7%[e]	79	82	86[f]	86[f]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	171	174	174	172
Change at Week 40[b]	-49	-55	-59	-60
Body Weight (kg)				
Baseline (mean)	93.7	92.5	94.8	93.8
Change at Week 40[b]	-5.7	-7.6	-9.3	-11.2
Difference from semaglutide[b] (95% CI)	--	-1.9[c] (-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 because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 3%, 2%, 1%, and 1% of patients randomized to semaglutide 1 mg, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. At Week 40 the HbA1c endpoint was missing for 5%, 4%, 5%, and 5% of patients randomized to semaglutide 1 mg, MOUNJARO 5 mg, 10 mg, and 15 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.

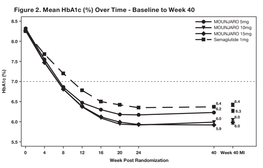
[c] p<0.05 (two-sided) for superiority vs. semaglutide, adjusted for multiplicity.

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

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

[f] p<0.01 (two-sided) for superiority vs. semaglutide, adjusted for multiplicity.

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



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).

Add-on to metformin with or without SGLT2 inhibitor

SURPASS-3 (NCT03882970) was a 52-week open-label trial that randomized 1444 adult patients with type 2 diabetes mellitus with inadequate glycemic control on stable doses of metformin with or without SGLT2 inhibitor to the addition of MOUNJARO 5 mg, MOUNJARO 10 mg, MOUNJARO 15 mg once weekly, or insulin degludec 100 units/mL once daily. In this trial, 32% of patients were on SGLT2 inhibitor. Insulin degludec was initiated at 10 units once daily and adjusted weekly throughout the trial using a treat-to-target algorithm based on self-measured fasting blood glucose values. At Week 52, 26% of patients randomized to insulin degludec achieved the fasting serum glucose target of <90 mg/dL, and the mean daily insulin degludec dose was 49 U (0.5 U per kilogram).

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 baseline 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 5).

Table 5: Results at Week 52 in a Trial of MOUNJARO versus Insulin Degludec in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin with or without SGLT2 Inhibitor

	Insulin Degludec	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg
Modified Intent-to-Treat (mITT)[a] Population (N)	359	358	360	358
HbA1c (%)				
Baseline (mean)	8.1	8.2	8.2	8.2
Change at Week 52[b]	-1.3	-1.9	-2.0	-2.1
Difference from insulin degludec[b] (95% CI)	--	-0.6[c] (-0.7, -0.5)	-0.8[c] (-0.9, -0.6)	-0.9[c] (-1.0, -0.7)
Patients (%) achieving HbA1c <7%[d]	58	79[c]	82[c]	83[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	167	172	170	168
Change at Week 52[b]	-51	-47	-50	-54
Body Weight (kg)				
Baseline (mean)	94.0	94.4	93.8	94.9
Change at Week 52[b]	1.9	-7.0	-9.6	-11.3
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 because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 1%,1%, 1%, and 2% of patients randomized to insulin degludec, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. At Week 52 the HbA1c endpoint was missing for 9%, 6%, 10%, and 5% of patients randomized to insulin degludec, MOUNJARO 5 mg, 10 mg, and 15 mg, 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 (two-sided) for superiority vs. insulin degludec, adjusted for multiplicity.

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

Add-on to 1-3 oral anti-hyperglycemic agents (metformin, sulfonylurea or SGLT-2 inhibitor)

SURPASS-4 (NCT03730662) was a 104-week open-label trial (52-week primary endpoint) that randomized 2002 adult patients with type 2 diabetes mellitus with increased cardiovascular risk to MOUNJARO 5 mg, MOUNJARO 10 mg, MOUNJARO 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 SGLT2 inhibitors (25%).

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 baseline 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% had a history of cardiovascular disease. 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.

Insulin glargine was initiated at 10 U once daily and adjusted weekly throughout the trial using a treat-to-target algorithm based on self-measured fasting blood glucose values. At Week 52, 30% of patients randomized to insulin glargine achieved the fasting serum glucose target of <100 mg/dL, and the mean daily insulin glargine dose was 44 U (0.5 U per kilogram).

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 6).

Table 6: Results at Week 52 in a Trial of MOUNJARO versus Insulin Glargine in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin and/or Sulfonylurea and/or SGLT2 Inhibitor

	Insulin Glargine	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	998	328	326	337
HbA1c (%)				
Baseline (mean)	8.5	8.5	8.6	8.5
Change at Week 52[b]	-1.4	-2.1	-2.3	-2.4
Difference from insulin glargine[b] (95% CI)	--	-0.7[c] (-0.9, -0.6)	-0.9[c] (-1.1, -0.8)	-1.0[c] (-1.2, -0.9)
Patients (%) achieving HbA1c <7%[d]	49	75[c]	83[c]	85[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	168	172	176	174
Change at Week 52[b]	-49	-44	-50	-55
Body Weight (kg)				
Baseline (mean)	90.2	90.3	90.6	90.0
Change at Week 52[b]	1.7	-6.4	-8.9	-10.6
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 because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 1%, 0%, 0%, and 1% of patients randomized to insulin glargine, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. At Week 52 the HbA1c endpoint was missing for 9%, 9%, 6%, and 4% of patients randomized to insulin glargine, MOUNJARO 5 mg, 10 mg, and 15 mg, 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 (two-sided) for superiority vs. insulin glargine, adjusted for multiplicity.

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

14.4 MOUNJARO Use in Combination with Basal Insulin with or without Metformin in Adult Patients with Type 2 Diabetes Mellitus

SURPASS-5 (NCT04039503) was a 40-week double-blind trial that randomized 475 patients with type 2 diabetes mellitus with inadequate glycemic control on insulin glargine 100 units/mL, with or without metformin, to MOUNJARO 5 mg, MOUNJARO 10 mg, MOUNJARO 15 mg once weekly, or placebo. The dose of background insulin glargine was adjusted using a treat-to-target algorithm based on self-measured fasting blood glucose values, targeting <100 mg/dL.

Patients had a mean age of 61 years, and 56% were men. The mean duration of type 2 diabetes mellitus was 13.3 years, and the mean baseline BMI was 33 kg/m^2. Overall, 80% were White, 11% were Black or African American, and 18% were Asian; 5% identified as Hispanic or Latino ethnicity.

The mean dose of insulin glargine at baseline was 34, 32, 35, and 33 units/day for patients receiving 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 once weekly, 10 mg once weekly and 15 mg once weekly for 40 weeks resulted in a statistically significant reduction in HbA1c compared with placebo (see Table 7).

Table 7: Results at Week 40 in a Trial of MOUNJARO Added to Basal Insulin with or without Metformin in Adult Patients with Type 2 Diabetes Mellitus

	Placebo	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	119	116	118	118
HbA1c (%)				
Baseline (mean)	8.4	8.3	8.4	8.2
Change at Week 40[b]	-0.9	-2.1	-2.4	-2.3
Difference from placebo[b] (95% CI)	--	-1.2[c] (-1.5, -1.0)	-1.5[c] (-1.8, -1.3)	-1.5[c] (-1.7, -1.2)
Patients (%) achieving HbA1c <7%[d]	35	87[c]	90[c]	85[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	164	163	163	160
Change at Week 40[b]	-39	-58	-64	-63
Difference from placebo[b] (95% CI)	--	-19[c] (-27, -11)	-25[c] (-32, -17)	-23[c] (-31, -16)
Body Weight (kg)				
Baseline (mean)	94.2	95.8	94.6	96.0
Change at Week 40[b]	1.6	-5.4	-7.5	-8.8
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 because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 4%, 1%, 1%, 0%, and 1% of patients randomized to placebo, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. At Week 40 the HbA1c endpoint was missing for 2%, 6%, 3%, and 7% of patients randomized to placebo, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. Missing Week 40 data were imputed using placebo-based multiple imputation.

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MOUNJARO is a clear, colorless to slightly yellow solution available in pre-filled single-dose pens as follows:

Total Strength per Total Volume	Carton Contents
2.5 mg/0.5 mL	4 single-dose pens
5 mg/0.5 mL	4 single-dose pens
7.5 mg/0.5 mL	4 single-dose pens
10 mg/0.5 mL	4 single-dose pens
12.5 mg/0.5 mL	4 single-dose pens
15 mg/0.5 mL	4 single-dose pens

Not all strengths, pack sizes or presentations may be marketed.

16.2 Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the approved *Package insert and Instructions for Use.*

Risk of Thyroid C-Cell Tumors

Inform patients that MOUNJARO causes thyroid C-cell tumors in rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, persistent hoarseness, dysphagia, or dyspnea) to their healthcare provider *[see Boxed Warning and Warnings and Precautions (5.1)].*

Mounjaro™ (tirzepatide)
Injection, for subcutaneous use

Pancreatitis

Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue MOUNJARO promptly and contact their healthcare provider if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting) *[see Warnings and Precautions (5.2)].*

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Inform patients that the risk of hypoglycemia is increased when MOUNJARO is used with an insulin secretagogue (such as a sulfonylurea) or insulin. Educate patients on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.3)].*

Hypersensitivity Reactions

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

Acute Kidney Injury

Advise patients treated with MOUNJARO of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs *[see Warnings and Precautions (5.5)].*

Severe Gastrointestinal Adverse Reactions

Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms *[see Warnings and Precautions (5.6)].*

Diabetic Retinopathy Complications

Inform patients to contact their healthcare provider if changes in vision are experienced during treatment with MOUNJARO *[see Warnings and Precautions (5.7)].*

Acute Gallbladder Disease

Inform patients of the risk of acute gallbladder disease. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected *[see Warnings and Precautions (5.8)].*

Pregnancy

Advise a pregnant woman of the potential risk to a fetus. Advise women to inform their healthcare provider if they are pregnant or intend to become pregnant *[see Use in Specific Populations (8.1)].*

Contraception

Use of MOUNJARO may reduce the efficacy of oral hormonal contraceptives. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO *[see Drug Interactions (7.2), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)].*

Missed Doses

Inform patients if a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, inform patients to resume their regular once weekly dosing schedule *[see Dosage and Administration (2.1)].*

Manufactured and packaged by:

Eli Lilly and Company

Indianapolis, IN 46285, USA

Prescription only.

WARNING: RISK OF THYROID C-CELL TUMORS

- **In both male and female rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **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) *[see Contraindications (4)]*. 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). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with MOUNJARO *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

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

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

- The recommended starting dosage of MOUNJARO is 2.5 mg injected subcutaneously once weekly. The 2.5 mg dosage is for treatment initiation and is not intended for glycemic control.
- After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly.
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The maximum dosage of MOUNJARO is 15 mg injected subcutaneously once weekly.
- If a dose is missed, instruct patients to administer MOUNJARO 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.
- The day of weekly administration can be changed, if necessary, as long as the time between the two doses is at least 3 days (72 hours).

2.2 Important Administration Instructions

- Administer MOUNJARO once weekly, any time of day, with or without meals.
- Inject MOUNJARO subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.
- Inspect MOUNJARO visually before use. It should appear clear and colorless 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.
- In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

3 DOSAGE FORMS AND STRENGTHS

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

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

Not all strengths, pack sizes or presentations may be marketed.

4 CONTRAINDICATIONS

MOUNJARO is contraindicated in patients with:

- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Warnings and Precautions (5.1)]*.
- Known serious hypersensitivity to tirzepatide or any of the excipients in MOUNJARO *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors

In both sexes of rats, tirzepatide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) in a 2-year study at clinically relevant plasma exposures *[see Nonclinical Toxicology (13.1)]*. It is unknown whether MOUNJARO causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined.

MOUNJARO is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of MOUNJARO and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with MOUNJARO. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin values may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists.

In clinical studies, 14 events of acute pancreatitis were confirmed by adjudication in 13 MOUNJARO-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 comparator-treated patients (0.11 patients per 100 years of exposure). MOUNJARO has not been studied in patients with a prior history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on MOUNJARO.

After initiation of MOUNJARO, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue MOUNJARO and initiate appropriate management.

5.3 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients receiving MOUNJARO in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia *[see Adverse Reactions (6.1), Drug Interactions (7.1)]*.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

5.4 Hypersensitivity Reactions

Hypersensitivity reactions have been reported with MOUNJARO in clinical trials (e.g., urticaria and eczema) and were sometimes severe. 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 serious hypersensitivity reaction to tirzepatide or any of the excipients in MOUNJARO *[see Contraindications (4)]*.

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

5.5 Acute Kidney Injury

MOUNJARO has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhea *[see Adverse Reactions (6.1)]*. These events may lead to dehydration, which if severe could cause acute kidney injury.

In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of MOUNJARO in patients with renal impairment reporting severe gastrointestinal adverse reactions.

5.6 Severe Gastrointestinal Disease

Use of MOUNJARO has been associated with gastrointestinal adverse reactions, sometimes severe *[see Adverse Reactions 6.1]*. MOUNJARO has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

5.7 Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy

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

5.8 Acute Gallbladder Disease

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

In MOUNJARO placebo-controlled clinical trials, acute gallbladder disease (cholelithiasis, 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin *[see Warnings and Precautions (5.3)]*
- Hypersensitivity *[see Warnings and Precautions (5.4)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.5)]*
- Severe Gastrointestinal Disease *[see Warnings and Precautions (5.6)]*
- Diabetic Retinopathy Complications *[see Warnings and Precautions (5.7)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pool of Two Placebo-Controlled Clinical Trials

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

Pool of Seven Controlled Clinical Trials

Adverse reactions were also evaluated in a larger pool of adult patients with type 2 diabetes mellitus participating in seven controlled clinical trials which included two placebo-controlled trials (SURPASS-1 and -5), three trials of MOUNJARO in combination with metformin, sulfonylureas, and/or SGLT2 Inhibitors (SURPASS-2, -3, -4) *[see Clinical Studies (14.3)]* and two additional trials conducted in Japan. In this pool, a total of 5119 adult patients with type 2 diabetes mellitus were treated with MOUNJARO for a mean duration of 48.1 weeks. The mean age of patients was 58 years, 4% were 75 years or older and 58% were male. The population was 65% White, 24% Asian, 7% American Indian or Alaska Native, and 3% Black or African American; 38% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes mellitus for an average of 9.1 years with a mean HbA1c of 8.3%. As assessed by baseline fundoscopic examination, 15% of the population had retinopathy. At baseline, eGFR was ≥90 mL/min/1.73 m^2 in 52%, 60 to 90 mL/min/1.73 m^2 in 40%, 45 to 60 mL/min/1.73 m^2 in 6%, and 30 to 45 mL/min/1.73 m^2 in 1% of patients.

Common Adverse Reactions

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

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

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

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

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

Gastrointestinal Adverse Reactions

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

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

Other Adverse Reactions

Hypoglycemia

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

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

	Placebo %	MOUNJARO 5 mg %	MOUNJARO 10 mg %	MOUNJARO 15 mg %
Monotherapy				
(40 weeks)*	N=115	N=121	N=119	N=120
Blood glucose <54 mg/dL	1	0	0	0
Severe hypoglycemia**	0	0	0	0
Add-on to Basal Insulin with or without Metformin				
(40 weeks)*	N=120	N=116	N=119	N=120
Blood glucose <54 mg/dL	13	16	19	14
Severe hypoglycemia**	0	0	2	1

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

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

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

Heart Rate Increase

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

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with MOUNJARO in the pool of placebo-controlled trials, sometimes severe (e.g., urticaria and eczema); 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 Clinical Pharmacology (12.6)]*.

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 *[see Clinical Pharmacology (12.6)]*.

Acute Gallbladder Disease

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

Laboratory Abnormalities

Amylase and Lipase Increase

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

7 DRUG INTERACTIONS

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

When initiating MOUNJARO, consider reducing the dose of concomitantly administered insulin secretagogues (e.g., sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.3)]*.

7.2 Oral Medications

MOUNJARO delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with MOUNJARO.

Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with MOUNJARO.

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. Hormonal contraceptives that are not administered orally should not be affected *[see Use in Specific Populations (8.3) and Clinical Pharmacology (12.2, 12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with MOUNJARO use in pregnant women are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. MOUNJARO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered tirzepatide during organogenesis, fetal growth reductions and fetal abnormalities occurred at clinical exposure in maternal rats based on AUC. In rabbits administered tirzepatide during organogenesis, fetal growth reductions were observed at clinically relevant exposures based on AUC. These adverse embryo/fetal effects in animals coincided with pharmacological effects on maternal weight and food consumption *(see Data)*.

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA1c >7% and has been reported to be as high as 20–25% in women with an HbA1c >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

Data

Animal Data

In pregnant rats given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide (0.03-, 0.07-, and 0.5-fold the MRHD of 15 mg once weekly based on AUC) during organogenesis, increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and decreased fetal weights coincided with pharmacologically-mediated reductions in maternal body weights and food consumption at 0.5 mg/kg. In pregnant rabbits given once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg tirzepatide (0.01-, 0.06-, and 0.2-fold the MRHD) during organogenesis, pharmacologically-mediated effects on the gastrointestinal system resulting in maternal mortality or abortion in a few rabbits occurred at all dose levels. Reduced fetal weights associated with decreased maternal food consumption and body weights were observed at 0.1 mg/kg. In a pre- and post-natal study in rats administered subcutaneous doses of 0.02, 0.10, or 0.25 mg/kg tirzepatide twice weekly from implantation through lactation, F_1 pups from F_0 maternal rats given 0.25 mg/kg tirzepatide had statistically significant lower mean body weight when compared to controls from post-natal day 7 through post-natal day 126 for males and post-natal day 56 for females.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

Use of MOUNJARO may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying. This delay is largest after the first dose and diminishes over time. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO *[see Drug Interactions (7.2) and Clinical Pharmacology (12.2, 12.3)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the pool of seven clinical trials, 1539 (30.1%) 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.

8.6 Renal Impairment

No dosage adjustment of MOUNJARO is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no change in tirzepatide pharmacokinetics (PK) was observed *[see Clinical Pharmacology (12.3)]*. Monitor renal function when initiating or escalating doses of MOUNJARO in patients with renal impairment reporting severe adverse gastrointestinal reactions *[see Warnings and Precautions (5.5)]*.

8.7 Hepatic Impairment

No dosage adjustment of MOUNJARO is recommended for patients with hepatic impairment. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no change in tirzepatide PK was observed *[see Clinical Pharmacology (12.3)]*.

9.0 Effects on the Ability to Drive and Use Machines

No studies on the effects of 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 hypoglycemia while driving and using machines.

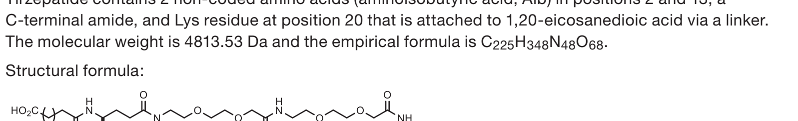
10 OVERDOSAGE

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

11 DESCRIPTION

MOUNJARO (tirzepatide) injection, for subcutaneous use, contains tirzepatide, a once weekly GIP receptor and GLP-1 receptor agonist. It is a 39-amino-acid modified peptide based on the GIP sequence. Tirzepatide contains 2 non-coded amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 that is attached to 1,20-eicosanedioic acid via a linker. The molecular weight is 4813.53 Da and the empirical formula is $C_{225}H_{348}N_{48}O_{68}$.

Structural formula:



MOUNJARO is a clear, colorless to slightly yellow, sterile, preservative-free solution for subcutaneous use. Each single-dose pen contains a 0.5 mL solution of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg of tirzepatide and the following excipients: sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. MOUNJARO has a pH of 6.5 – 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It is a 39-amino-acid modified peptide with a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.

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

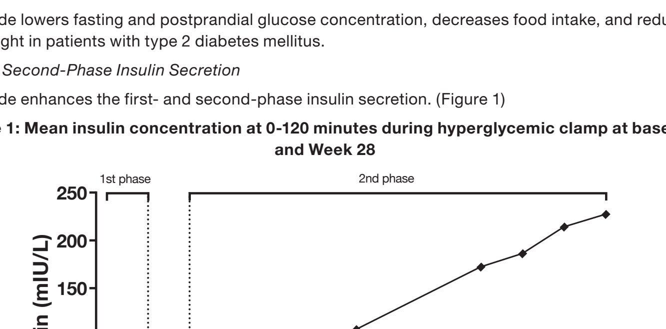
12.2 Pharmacodynamics

Tirzepatide lowers fasting and postprandial glucose concentration, decreases food intake, and reduces body weight in patients with type 2 diabetes mellitus.

First and Second-Phase Insulin Secretion

Tirzepatide enhances the first- and second-phase insulin secretion. (Figure 1)

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



Insulin Sensitivity

Tirzepatide increases insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study after 28 weeks of treatment.

Glucagon Secretion

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

Gastric Emptying

Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time. Tirzepatide slows post-meal glucose absorption, reducing postprandial glucose.

12.3 Pharmacokinetics

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with type 2 diabetes mellitus. Steady-state plasma tirzepatide concentrations were achieved following 4 weeks of once weekly administration. Tirzepatide exposure increases in a dose-proportional manner.

Absorption

Following subcutaneous administration, the time to maximum plasma concentration of tirzepatide ranges from 8 to 72 hours. The mean absolute bioavailability of tirzepatide following subcutaneous administration is 80%. Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm.

Distribution

The mean apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with type 2 diabetes mellitus is approximately 10.3 L. Tirzepatide is highly bound to plasma albumin (99%).

Elimination

The apparent population mean clearance of tirzepatide is 0.061 L/h with an elimination half-life of approximately 5 days, enabling once-weekly dosing.

Metabolism

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

Excretion

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

Specific Populations

The intrinsic factors of age, gender, race, ethnicity, or body weight do not have a clinically relevant effect on the PK of tirzepatide.

Patients with Renal Impairment

Renal impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. This was also shown for patients with both type 2 diabetes mellitus and renal impairment based on data from clinical studies *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

Hepatic impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function *[see Use in Specific Populations (8.7)]*.

Drug Interactions Studies

Potential for Tirzepatide to Influence the Pharmacokinetics of Other Drugs

In vitro studies have shown low potential for tirzepatide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

MOUNJARO delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications *[see Drug Interactions (7.2)]*.

The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses.

Following a first dose of tirzepatide 5 mg, acetaminophen maximum concentration (C_{max}) was reduced by 50%, and the median peak plasma concentration (t_{max}) occurred 1 hour later. After coadministration at week 4, there was no meaningful impact on acetaminophen C_{max} and t_{max}. Overall acetaminophen exposure (AUC_{0-24hr}) was not influenced.

Following administration of a combined oral contraceptive (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single dose of tirzepatide 5 mg, mean C_{max} of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%,66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in t_{max} of 2.5 to 4.5 hours was observed.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the trials described below with the incidence of anti-drug antibodies in other trials, including those of tirzepatide or of GLP-1 receptor agonist products.

During the 40- to 104-week treatment periods with ADA sampling conducted up to 44 to 108 weeks in seven clinical trials in adults with type 2 diabetes mellitus *[see Clinical Studies (14)]*, 51% (2,570/5,025) of MOUNJARO-treated patients developed anti-tirzepatide antibodies. In these trials, anti-tirzepatide antibody formation in 34% and 14% of MOUNJARO-treated patients showed cross-reactivity to native GIP or native GLP-1, respectively.

Of the 2,570 MOUNJARO-treated patients who developed anti-tirzepatide antibodies during the treatment periods in these seven trials, 2% and 2% developed neutralizing antibodies against tirzepatide activity on the GIP or GLP-1 receptors, respectively, and 0.9% and 0.4% developed neutralizing antibodies against native GIP or GLP-1, respectively.

There was no identified clinically significant effect of anti-tirzepatide antibodies on pharmacokinetics or effectiveness of MOUNJARO. More MOUNJARO-treated patients who developed anti-tirzepatide antibodies experienced hypersensitivity reactions or injection site reactions than those who did not develop these antibodies *[see Adverse Reactions (6.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.1-, 0.4-, and 1-fold the MRHD of 15 mg once weekly based on AUC) administered by subcutaneous injection twice weekly. A statistically significant increase in thyroid C-cell adenomas was observed in males (≥0.5 mg/kg) and females (≥0.15 mg/kg), and a statistically significant increase in thyroid C-cell adenomas and carcinomas combined was observed in males and females at all doses examined. In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered by subcutaneous injection twice weekly was not tumorigenic.

Tirzepatide was not genotoxic in a rat bone marrow micronucleus assay.

In fertility and early embryonic development studies, male and female rats were administered twice weekly subcutaneous doses of 0.5, 1.5, or 3 mg/kg (0.3-, 1-, and 2-fold and 0.3-, 0.9-, and 2-fold, respectively, the MRHD of 15 mg once weekly based on AUC). No effects of tirzepatide were observed on sperm morphology, mating, fertility, and conception. In female rats, an increase in the number of females with prolonged diestrus and a decrease in the mean number of corpora lutea resulting in a decrease in the mean number of implantation sites and viable embryos was observed at all dose levels. These effects were considered secondary to the pharmacological effects of tirzepatide on food consumption and body weight.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The effectiveness of MOUNJARO as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus was established in five trials. In these trials, MOUNJARO was studied as monotherapy (SURPASS-1); as an add-on to metformin, sulfonylureas, and/or sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) (SURPASS-2, -3, and -4); and in combination with basal insulin with or without metformin (SURPASS-5). In these trials, MOUNJARO (5 mg, 10 mg, and 15 mg given subcutaneously once weekly) was compared with placebo, semaglutide 1 mg, insulin degludec, and/or insulin glargine.

In adult patients with type 2 diabetes mellitus, treatment with MOUNJARO produced a statistically significant reduction from baseline in HbA1c compared to placebo. The effectiveness of MOUNJARO was not impacted by age, gender, race, ethnicity, region, or by baseline BMI, HbA1c, diabetes duration, or renal function.

14.2 Monotherapy Use of MOUNJARO in Adult Patients with Type 2 Diabetes Mellitus

SURPASS-1 (NCT03954834) was a 40-week double-blind trial that randomized 478 adult patients with type 2 diabetes mellitus with inadequate glycemic control with diet and exercise to MOUNJARO 5 mg, MOUNJARO 10 mg, MOUNJARO 15 mg, or placebo once weekly.

Patients had a mean age of 54 years, and 52% were men. The mean duration of type 2 diabetes mellitus was 4.7 years, and the mean BMI was 32 kg/m^2. Overall, 36% were White, 35% were Asian, 25% were American Indians/Alaska Natives, and 5% were Black or African American; 43% identified as Hispanic or Latino ethnicity.

Monotherapy with 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 3).

Table 3: 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

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

[a] The modified intent-to-treat population consists of all randomly assigned participants who were exposed to at least 1 dose of study drug. Patients who discontinued study treatment because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 25%, 2%, 3%, and 2% of patients randomized to placebo, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. At Week 40 the HbA1c data were missing for 12%, 6%, 7%, and 14% of patients randomized to placebo, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. Missing Week 40 data were imputed using placebo-based multiple imputation.

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

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

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

14.3 MOUNJARO Use in Combination with Metformin, Sulfonylureas, and/or SGLT2 Inhibitors in Adult Patients with Type 2 Diabetes Mellitus

Add-on to metformin

SURPASS-2 (NCT03987919) was a 40-week open-label trial (double-blind with respect to MOUNJARO dose assignment) that randomized 1879 adult patients with type 2 diabetes mellitus with inadequate glycemic control on stable doses of metformin alone to the addition of MOUNJARO 5 mg, MOUNJARO 10 mg, or MOUNJARO 15 mg once weekly or subcutaneous semaglutide 1 mg once weekly.

Patients had a mean age of 57 years and 47% were men. The mean duration of type 2 diabetes mellitus was 8.6 years, and the mean BMI was 34 kg/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 4 and Figure 2).

Table 4: Results at Week 40 in a Trial of MOUNJARO versus Semaglutide 1 mg in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin

	Semaglutide 1 mg	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	468	470	469	469
HbA1c (%)				
Baseline (mean)	8.3	8.3	8.3	8.3
Change at Week 40[b]	-1.9	-2.0	-2.2	-2.3
Difference from semaglutide[b] (95% CI)	--	-0.2[c] (-0.3, -0.0)	-0.4[d] (-0.5, -0.3)	-0.5[d] (-0.6, -0.3)
Patients (%) achieving HbA1c <7%[e]	79	82	86[f]	86[f]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	171	174	174	172
Change at Week 40[b]	-49	-55	-59	-60
Body Weight (kg)				
Baseline (mean)	93.7	92.5	94.8	93.8
Change at Week 40[b]	-5.7	-7.6	-9.3	-11.2
Difference from semaglutide[b] (95% CI)	--	-1.9[c] (-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 because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 3%, 2%, 1%, and 1% of patients randomized to semaglutide 1 mg, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. At Week 40 the HbA1c endpoint was missing for 5%, 4%, 5%, and 5% of patients randomized to semaglutide 1 mg, MOUNJARO 5 mg, 10 mg, and 15 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.

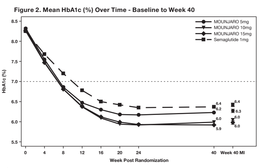
[c] p<0.05 (two-sided) for superiority vs. semaglutide, adjusted for multiplicity.

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

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

[f] p<0.01 (two-sided) for superiority vs. semaglutide, adjusted for multiplicity.

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



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).

Add-on to metformin with or without SGLT2 inhibitor

SURPASS-3 (NCT03882970) was a 52-week open-label trial that randomized 1444 adult patients with type 2 diabetes mellitus with inadequate glycemic control on stable doses of metformin with or without SGLT2 inhibitor to the addition of MOUNJARO 5 mg, MOUNJARO 10 mg, MOUNJARO 15 mg once weekly, or insulin degludec 100 units/mL once daily. In this trial, 32% of patients were on SGLT2 inhibitor. Insulin degludec was initiated at 10 units once daily and adjusted weekly throughout the trial using a treat-to-target algorithm based on self-measured fasting blood glucose values. At Week 52, 26% of patients randomized to insulin degludec achieved the fasting serum glucose target of <90 mg/dL, and the mean daily insulin degludec dose was 49 U (0.5 U per kilogram).

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 baseline 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 5).

Table 5: Results at Week 52 in a Trial of MOUNJARO versus Insulin Degludec in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin with or without SGLT2 Inhibitor

	Insulin Degludec	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg
Modified Intent-to-Treat (mITT)[a] Population (N)	359	358	360	358
HbA1c (%)				
Baseline (mean)	8.1	8.2	8.2	8.2
Change at Week 52[b]	-1.3	-1.9	-2.0	-2.1
Difference from insulin degludec[b] (95% CI)	--	-0.6[c] (-0.7, -0.5)	-0.8[c] (-0.9, -0.6)	-0.9[c] (-1.0, -0.7)
Patients (%) achieving HbA1c <7%[d]	58	79[c]	82[c]	83[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	167	172	170	168
Change at Week 52[b]	-51	-47	-50	-54
Body Weight (kg)				
Baseline (mean)	94.0	94.4	93.8	94.9
Change at Week 52[b]	1.9	-7.0	-9.6	-11.3
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 because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 1%,1%, 1%, and 2% of patients randomized to insulin degludec, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. At Week 52 the HbA1c endpoint was missing for 9%, 9%, 10%, and 5% of patients randomized to insulin degludec, MOUNJARO 5 mg, 10 mg, and 15 mg, 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 (two-sided) for superiority vs. insulin degludec, adjusted for multiplicity.

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

Add-on to 1-3 oral anti-hyperglycemic agents (metformin, sulfonylurea or SGLT-2 inhibitor)

SURPASS-4 (NCT03730662) was a 104-week open-label trial (52-week primary endpoint) that randomized 2002 adult patients with type 2 diabetes mellitus with increased cardiovascular risk to MOUNJARO 5 mg, MOUNJARO 10 mg, MOUNJARO 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 SGLT2 inhibitors (25%).

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 baseline 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% had a history of cardiovascular disease. 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.

Insulin glargine was initiated at 10 U once daily and adjusted weekly throughout the trial using a treat-to-target algorithm based on self-measured fasting blood glucose values. At Week 52, 30% of patients randomized to insulin glargine achieved the fasting serum glucose target of <100 mg/dL, and the mean daily insulin glargine dose was 44 U (0.5 U per kilogram).

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 6).

Table 6: Results at Week 52 in a Trial of MOUNJARO versus Insulin Glargine in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin and/or Sulfonylurea and/or SGLT2 Inhibitor

	Insulin Glargine	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	998	328	326	337
HbA1c (%)				
Baseline (mean)	8.5	8.5	8.6	8.5
Change at Week 52[b]	-1.4	-2.1	-2.3	-2.4
Difference from insulin glargine[b] (95% CI)	--	-0.7[c] (-0.9, -0.6)	-0.9[c] (-1.1, -0.8)	-1.0[c] (-1.2, -0.9)
Patients (%) achieving HbA1c <7%[d]	49	75[c]	83[c]	85[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	168	172	176	174
Change at Week 52[b]	-49	-44	-50	-55
Body Weight (kg)				
Baseline (mean)	90.2	90.3	90.6	90.0
Change at Week 52[b]	1.7	-6.4	-8.9	-10.6
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 because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 1%, 0%, 0%, and 1% of patients randomized to insulin glargine, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. At Week 52 the HbA1c endpoint was missing for 9%, 9%, 6%, and 4% of patients randomized to insulin glargine, MOUNJARO 5 mg, 10 mg, and 15 mg, 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 (two-sided) for superiority vs. insulin glargine, adjusted for multiplicity.

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

14.4 MOUNJARO Use in Combination with Basal Insulin with or without Metformin in Adult Patients with Type 2 Diabetes Mellitus

SURPASS-5 (NCT04039503) was a 40-week double-blind trial that randomized 475 patients with type 2 diabetes mellitus with inadequate glycemic control on insulin glargine 100 units/mL, with or without metformin, to MOUNJARO 5 mg, MOUNJARO 10 mg, MOUNJARO 15 mg once weekly, or placebo. The dose of background insulin glargine was adjusted using a treat-to-target algorithm based on self-measured fasting blood glucose values, targeting <100 mg/dL.

Patients had a mean age of 61 years, and 56% were men. The mean duration of type 2 diabetes mellitus was 13.3 years, and the mean baseline BMI was 33 kg/m^2. Overall, 80% were White, 11% were Black or African American, and 18% were Asian; 5% identified as Hispanic or Latino ethnicity.

The mean dose of insulin glargine at baseline was 34, 32, 35, and 33 units/day for patients receiving 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 once weekly, 10 mg once weekly and 15 mg once weekly for 40 weeks resulted in a statistically significant reduction in HbA1c compared with placebo (see Table 7).

Table 7: Results at Week 40 in a Trial of MOUNJARO Added to Basal Insulin with or without Metformin in Adult Patients with Type 2 Diabetes Mellitus

	Placebo	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	119	116	118	118
HbA1c (%)				
Baseline (mean)	8.4	8.3	8.4	8.2
Change at Week 40[b]	-0.9	-2.1	-2.4	-2.3
Difference from placebo[b] (95% CI)	--	-1.2[c] (-1.5, -1.0)	-1.5[c] (-1.8, -1.3)	-1.5[c] (-1.7, -1.2)
Patients (%) achieving HbA1c <7%[d]	35	87[c]	90[c]	85[c]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	164	163	163	160
Change at Week 40[b]	-39	-58	-64	-63
Difference from placebo[b] (95% CI)	--	-19[c] (-27, -11)	-25[c] (-32, -17)	-23[c] (-31, -16)
Body Weight (kg)				
Baseline (mean)	94.2	95.8	94.6	96.0
Change at Week 40[b]	1.6	-5.4	-7.5	-8.8
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 because they did not meet study enrollment criteria were excluded. During the trial, rescue medication (additional antihyperglycemic medication) was initiated by 4%, 1%, 1%, 0%, and 1% of patients randomized to placebo, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. At Week 40 the HbA1c endpoint was missing for 2%, 6%, 3%, and 7% of patients randomized to placebo, MOUNJARO 5 mg, 10 mg, and 15 mg, respectively. Missing Week 40 data were imputed using placebo-based multiple imputation.

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MOUNJARO is a clear, colorless to slightly yellow solution available in pre-filled single-dose pens as follows:

Total Strength per Total Volume	Carton Contents
2.5 mg/0.5 mL	4 single-dose pens
5 mg/0.5 mL	4 single-dose pens
7.5 mg/0.5 mL	4 single-dose pens
10 mg/0.5 mL	4 single-dose pens
12.5 mg/0.5 mL	4 single-dose pens
15 mg/0.5 mL	4 single-dose pens

Not all strengths, pack sizes or presentations may be marketed.

16.2 Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the approved *Package insert and Instructions for Use.*

Risk of Thyroid C-Cell Tumors

Inform patients that MOUNJARO causes thyroid C-cell tumors in rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, persistent hoarseness, dysphagia, or dyspnea) to their healthcare provider *[see Boxed Warning and Warnings and Precautions (5.1)].*

Mounjaro™ (tirzepatide)
Injection, for subcutaneous use

Pancreatitis

Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue MOUNJARO promptly and contact their healthcare provider if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting) *[see Warnings and Precautions (5.2)].*

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Inform patients that the risk of hypoglycemia is increased when MOUNJARO is used with an insulin secretagogue (such as a sulfonylurea) or insulin. Educate patients on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.3)].*

Hypersensitivity Reactions

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

Acute Kidney Injury

Advise patients treated with MOUNJARO of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs *[see Warnings and Precautions (5.5)].*

Severe Gastrointestinal Adverse Reactions

Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms *[see Warnings and Precautions (5.6)].*

Diabetic Retinopathy Complications

Inform patients to contact their healthcare provider if changes in vision are experienced during treatment with MOUNJARO *[see Warnings and Precautions (5.7).*

Acute Gallbladder Disease

Inform patients of the risk of acute gallbladder disease. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected *[see Warnings and Precautions (5.8)].*

Pregnancy

Advise a pregnant woman of the potential risk to a fetus. Advise women to inform their healthcare provider if they are pregnant or intend to become pregnant *[see Use in Specific Populations (8.1)].*

Contraception

Use of MOUNJARO may reduce the efficacy of oral hormonal contraceptives. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO *[see Drug Interactions (7.2), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)].*

Missed Doses

Inform patients if a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, inform patients to resume their regular once weekly dosing schedule *[see Dosage and Administration (2.1)].*

Manufactured by:
Vetter Pharma-Fertigung GmbH & Co. KG

Mooswiesen 2, Ravensburg, 88214 Germany

Prescription only.