ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 2.5 mg solution for injection in pre-filled pen
Mounjaro 5 mg solution for injection in pre-filled pen
Mounjaro 7.5 mg solution for injection in pre-filled pen
Mounjaro 10 mg solution for injection in pre-filled pen
Mounjaro 12.5 mg solution for injection in pre-filled pen
Mounjaro 15 mg solution for injection in pre-filled pen
Mounjaro 2.5 mg solution for injection in vial
Mounjaro 5 mg solution for injection in vial
Mounjaro 7.5 mg solution for injection in vial
Mounjaro 10 mg solution for injection in vial
Mounjaro 12.5 mg solution for injection in vial
Mounjaro 15 mg solution for injection in vial
Mounjaro 2.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 7.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 10 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 12.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 15 mg/dose KwikPen solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled pen, single-dose

Mounjaro 2.5 mg solution for injection in pre-filled pen
Each pre-filled pen contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml).

Mounjaro 5 mg solution for injection in pre-filled pen
Each pre-filled pen contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml).

Mounjaro 7.5 mg solution for injection in pre-filled pen
Each pre-filled pen contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml).

Mounjaro 10 mg solution for injection in pre-filled pen
Each pre-filled pen contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml).

Mounjaro 12.5 mg solution for injection in pre-filled pen
Each pre-filled pen contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml).

Mounjaro 15 mg solution for injection in pre-filled pen
Each pre-filled pen contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml).

Vial, single-dose

Mounjaro 2.5 mg solution for injection in vial
Each vial contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml).

Mounjaro 5 mg solution for injection in vial
Each vial contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml).

Mounjaro 7.5 mg solution for injection in vial
Each vial contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml).

Mounjaro 10 mg solution for injection in vial
Each vial contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml).

Mounjaro 12.5 mg solution for injection in vial
Each vial contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml).

Mounjaro 15 mg solution for injection in vial
Each vial contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml).

Pre-filled pen (KwikPen), multi-dose

Mounjaro 2.5 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 2.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 10 mg of tirzepatide in 2.4 ml (4.17 mg/ml). Each pen delivers 4 doses of 2.5 mg.

Mounjaro 5 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 20 mg of tirzepatide in 2.4 ml (8.33 mg/ml). Each pen delivers 4 doses of 5 mg.

Mounjaro 7.5 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 7.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 30 mg of tirzepatide in 2.4 ml (12.5 mg/ml). Each pen delivers 4 doses of 7.5 mg.

Mounjaro 10 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 10 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 40 mg of tirzepatide in 2.4 ml (16.7 mg/ml). Each pen delivers 4 doses of 10 mg.

Mounjaro 12.5 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 12.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 50 mg of tirzepatide in 2.4 ml (20.8 mg/ml). Each pen delivers 4 doses of 12.5 mg.

Mounjaro 15 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 15 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 60 mg of tirzepatide in 2.4 ml (25 mg/ml). Each pen delivers 4 doses of 15 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 diabetes mellitus

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

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and the populations studied, see sections 4.4, 4.5 and 5.1.

Weight management

Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥ 30 kg/m^2 (obesity) or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).

For trial results with respect to obstructive sleep apnoea (OSA), see section 5.1.

4.2 Posology and method of administration

Posology

The starting dose of tirzepatide is 2.5 mg once weekly. After 4 weeks, the dose should be increased to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose.

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

The maximum dose is 15 mg once weekly.

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

When tirzepatide is added to existing therapy of a sulphonylurea and/or insulin, a reduction in the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea and insulin. A stepwise approach to insulin reduction is recommended (see sections 4.4 and 4.8).

Missed doses

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, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

Changing the dosing schedule

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

Special populations

Elderly, gender, race, ethnicity or body weight
No dose adjustment is needed based on age, gender, race, ethnicity or body weight (see sections 5.1 and 5.2). Only very limited data are available from patients aged ≥ 85 years.

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

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

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

Method of administration

Mounjaro is to be injected subcutaneously in the abdomen, thigh or upper arm.

The dose can be administered at any time of day, with or without meals.

Injection sites should be rotated with each dose. If a patient also injects insulin, they should inject Mounjaro into a different injection site.

Patients should be advised to carefully read the instructions for use included with the package leaflet before administering the medicinal product.

Vial

Patients and their caregivers should be trained in subcutaneous injection technique before administering Mounjaro.

For further information before administration see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Acute pancreatitis

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

Acute pancreatitis has been reported in patients treated with tirzepatide.

Patients should be informed of the symptoms of acute pancreatitis. If pancreatitis is suspected, tirzepatide should be discontinued. If the diagnosis of pancreatitis is confirmed, tirzepatide should not be restarted. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis (see section 4.8).

Hypoglycaemia

Patients receiving tirzepatide in combination with an insulin secretagogue (for example, a sulphonylurea) or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of the insulin secretagogue or insulin (see sections 4.2 and 4.8).

Gastrointestinal effects

Tirzepatide has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhoea (see section 4.8). These adverse reactions may lead to dehydration, which could lead to a deterioration in renal function including acute renal failure. Patients treated with tirzepatide should be advised of the potential risk of dehydration, due to the gastrointestinal adverse reactions and take precautions to avoid fluid depletion and electrolyte disturbances. This should particularly be considered in the elderly, who may be more susceptible to such complications.

Severe gastrointestinal disease

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

Diabetic retinopathy

Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy or diabetic macular oedema, and should be used with caution in these patients with appropriate monitoring.

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 4.8) should be considered prior to performing procedures with general anaesthesia or deep sedation.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Benzyl alcohol

This medicinal product contains 5.4 mg benzyl alcohol in each 0.6 ml dose of Mounjaro KwikPen.

4.5 Interaction with other medicinal products and other forms of interaction

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

Based on the results from a study with paracetamol, which was used as a model medicinal product to evaluate the effect of tirzepatide on gastric emptying, no dose adjustments are expected to be required for most concomitantly administered oral medicinal products. However, it is recommended to monitor

patients on oral medicinal products with a narrow therapeutic index (e.g., warfarin, digoxin), especially at initiation of tirzepatide treatment and following dose increase. The risk of delayed effect should also be considered for oral medicinal products for which a rapid onset of effect is of importance.

Paracetamol

Following a 5 mg single dose of tirzepatide, the maximum plasma concentration (C_{max}) of paracetamol was reduced by 50 %, and the median (t_{max}) was delayed by 1 hour. The effect of tirzepatide on the oral absorption of paracetamol is dose and time dependent. At low doses (0.5 and 1.5 mg), there was only a minor change in paracetamol exposure. After four consecutive weekly doses of tirzepatide (5/5/8/10 mg), no effect on the paracetamol C_{max} and t_{max} was observed. The overall exposure (AUC) was not influenced. No dose adjustment of paracetamol is necessary when administered with tirzepatide.

Oral contraceptives

Administration of a combination oral contraceptive (0.035 mg ethinyl estradiol plus 0.25 mg norgestimate, a prodrug of norelgestromin) in the presence of a single dose of tirzepatide (5 mg) resulted in a reduction of oral contraceptive C_{max} and area under the curve (AUC). Ethinyl estradiol C_{max} was reduced by 59 % and AUC by 20 % with a delay in t_{max} of 4 hours. Norelgestromin C_{max} was reduced by 55 % and AUC by 23 % with a delay in t_{max} of 4.5 hours. Norgestimate C_{max} was reduced by 66 %, and AUC by 20 % with a delay in t_{max} of 2.5 hours. This reduction in exposure after a single dose of tirzepatide is not considered clinically relevant. No dose adjustment of oral contraceptives is required.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential are recommended to use contraception when treated with tirzepatide.

Pregnancy

There are no or a limited amount of data from the use of tirzepatide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Tirzepatide is not recommended during pregnancy and in women of childbearing potential not using contraception. If a patient wishes to become pregnant, or pregnancy occurs, tirzepatide should be discontinued. Tirzepatide should be discontinued at least 1 month before a planned pregnancy due to the long half-life (see section 5.2).

Breast-feeding

It is unknown whether tirzepatide is excreted in human milk. A risk to the newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tirzepatide therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of tirzepatide on fertility in humans is unknown.

Animal studies with tirzepatide did not indicate direct harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Tirzepatide has no or negligible influence on the ability to drive or use machines. When tirzepatide is used in combination with a sulphonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see section 4.4).

4.8 Undesirable effects

Summary of safety profile

In 12 completed phase 3 studies, 8 158 patients were exposed to tirzepatide alone or in combination with other glucose lowering medicinal products. The most frequently reported adverse reactions were gastrointestinal disorders and these were mostly mild or moderate in severity. The incidence of nausea, diarrhoea and vomiting was higher during the dose escalation period and decreased over time (see sections 4.2, and 4.4).

Tabulated list of adverse reactions

The following related adverse reactions from clinical studies are listed below by system organ class and in order of decreasing incidence (very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1 000 to < 1/100; rare: ≥ 1/10 000 to < 1/1 000; very rare: < 1/10 000). Within each incidence grouping, adverse reactions are presented in order of decreasing frequency.

Table 1. Adverse reactions

System organ class	Very common	Common	Uncommon	Rare
Immune system disorders		Hypersensitivity reactions		Anaphylactic reaction[#], Angioedema[#]
Metabolism and nutrition disorders	Hypoglycaemia[1]* when used with sulphonylurea or insulin	Hypoglycaemia[1]* when used with metformin and SGLT2i, Decreased appetite[1]	Hypoglycaemia[1]* when used with metformin, Weight decreased[1]	
Nervous system disorders		Dizziness[2]	Dysgeusia, Dysaesthesia	
Vascular disorders		Hypotension[2]		
Gastrointestinal disorders	Nausea, Diarrhoea, Vomiting[3], Abdominal pain[3], Constipation[3]	Dyspepsia, Abdominal distention, Eructation, Flatulence, Gastroesophageal reflux disease	Cholelithiasis, Cholecystitis, Acute pancreatitis, Delayed gastric emptying	
Skin and subcutaneous tissue disorders		Hair loss[2]		
General disorders and administration site conditions		Fatigue[†], Injection site reactions	Injection site pain	
Investigations		Heart rate increased, Lipase increased, Amylase increased, Blood calcitonin increased[4]		

[#]From post-marketing reports
*Hypoglycaemia defined below.
[†]Fatigue includes the terms fatigue, asthenia, malaise, and lethargy.
[1] Adverse reaction that only applies to patients with type 2 diabetes mellitus (T2DM).
[2] Adverse reaction that mainly applies to patients with overweight or obesity, with or without T2DM.
[3] Frequency was very common in weight management and OSA trials, and common in T2DM trials.
[4] Frequency was common in weight management trials, and uncommon in T2DM and OSA trials.

Description of selected adverse reactions

Hypersensitivity reactions

Hypersensitivity reactions have been reported with tirzepatide in the pool of T2DM placebo-controlled trials, sometimes severe (e.g., urticaria and eczema); hypersensitivity reactions were reported in 3.2 % of tirzepatide-treated patients compared to 1.7 % of placebo-treated patients. Cases of anaphylactic reaction and angioedema have been rarely reported with marketed use of tirzepatide.

Hypersensitivity reactions have been reported with tirzepatide in a pool of 3 placebo-controlled weight management trials and in a pool of 2 placebo-controlled OSA trials, sometimes severe (e.g., rash and dermatitis); hypersensitivity reactions were reported in 3.0 - 5.0 % of tirzepatide-treated patients compared to 2.1 - 3.8 % of placebo-treated patients.

Hypoglycaemia in patients with type 2 diabetes mellitus

Type 2 diabetes studies
Clinically significant hypoglycaemia (blood glucose < 3.0 mmol/L (< 54 mg/dL)) or severe hypoglycaemia (requiring the assistance of another person) occurred in 10 to 14 % (0.14 to 0.16 events/patient year) of patients when tirzepatide was added to sulphonylurea and in 14 to 19 % (0.43 to 0.64 events/patient year) of patients when tirzepatide was added to basal insulin.

The rate of clinically significant hypoglycaemia when tirzepatide was used as monotherapy or when added to other oral antidiabetic medicinal products was up to 0.04 events/patient year (see table 1 and sections 4.2, 4.4 and 5.1).

In phase 3 clinical studies, 10 (0.2 %) patients reported 12 episodes of severe hypoglycaemia. Of these 10 patients, 5 (0.1 %) were on a background of insulin glargine or sulphonylurea who reported 1 episode each.

Weight management study
In a placebo-controlled weight management phase 3 trial in patients with T2DM, hypoglycaemia (blood glucose < 3.0 mmol/L (< 54 mg/dL)) was reported in 4.2 % of tirzepatide-treated patients versus 1.3 % of placebo-treated patients. In this trial, patients taking tirzepatide in combination with an insulin secretagogue (e.g., sulfonylurea) had a higher incidence of hypoglycaemia (10.3 %) compared to tirzepatide-treated patients not taking a sulfonylurea (2.1 %). No severe hypoglycaemia episodes were reported.

Gastrointestinal adverse reactions

In the placebo-controlled T2DM phase 3 studies, gastrointestinal disorders were dose-dependently increased for tirzepatide 5 mg (37.1 %), 10 mg (39.6 %) and 15 mg (43.6 %) compared with placebo (20.4 %). Nausea occurred in 12.2 %, 15.4 % and 18.3 % versus 4.3 % and diarrhoea in 11.8 %, 13.3 % and 16.2 % versus 8.9 % for tirzepatide 5 mg, 10 mg and 15 mg versus placebo. Gastrointestinal adverse reactions were mostly mild (74 %) or moderate (23.3 %) in severity. The

incidence of nausea, vomiting, and diarrhoea was higher during the dose escalation period and decreased over time.

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

In a placebo-controlled weight management phase 3 study in patients without T2DM, gastrointestinal disorders were increased for tirzepatide 5 mg (55.6 %), 10 mg (60.8 %) and 15 mg (59.2 %) compared with placebo (30.3 %). Nausea occurred in 24.6 %, 33.3 % and 31.0 % versus 9.5 % and diarrhoea in 18.7 %, 21.2 % and 23.0 % versus 7.3 % for tirzepatide 5 mg, 10 mg and 15 mg respectively versus placebo. Gastrointestinal adverse reactions were mostly mild (60.8 %) or moderate (34.6 %) in severity. The incidence of nausea, vomiting, and diarrhoea was higher during the dose escalation period and decreased over time.

More patients in the tirzepatide 5 mg (1.9 %), 10 mg (4.4 %) and 15 mg (4.1 %) groups compared to the placebo group (0.5 %) discontinued study treatment permanently due to the gastrointestinal event.

Gallbladder-related events

In a pool of 3 placebo-controlled weight management phase 3 studies, the overall incidence of cholecystitis and cholecystitis acute was 0.6 % and 0.2 % for tirzepatide- and placebo-treated patients, respectively.

In a pool of 3 placebo-controlled weight management phase 3 studies and in a pool of 2 placebo-controlled OSA phase 3 studies, acute gallbladder disease was reported in up to 2.0 % of tirzepatide-treated patients and in up to 1.6 % of placebo-treated patients.

In the weight management phase 3 studies, acute gallbladder events were positively associated with weight reduction.

Immunogenicity

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

5 025 tirzepatide-treated patients in the T2DM phase 3 clinical studies were assessed for ADA. Of these, 51.1 % developed treatment-emergent (TE) ADA during the on-treatment period. In 38.3 % of the assessed patients, TE ADA were persistent (that is TE ADA present for a period of 16 weeks or greater). 1.9 % and 2.1 % had neutralising antibodies against tirzepatide activity on the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, respectively and 0.9 % and 0.4 % had neutralising antibodies against native GIP and native GLP-1, respectively.

3 710 tirzepatide-treated patients in the 4 phase 3 weight management and 2 phase 3 OSA studies were assessed for ADA. Of these, 60.6 - 65.1 % developed TE ADA during the on-treatment period. In 46.5 - 51.3 % of the assessed patients, TE ADA were persistent. Up to 2.3 % and 2.3 % had neutralising antibodies against tirzepatide activity on the GIP and GLP-1 receptors, respectively and up to 0.7 % and 0.1 % had neutralising antibodies against native GIP and native GLP-1, respectively.

Heart rate

In the placebo-controlled T2DM phase 3 studies, treatment with tirzepatide resulted in a maximum mean increase in heart rate of 3 to 5 beats per minute. The maximum mean increase in heart rate in placebo-treated patients was 1 beat per minute.

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

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

In 3 placebo-controlled weight management phase 3 studies, treatment with tirzepatide resulted in a mean increase in heart rate of 3 beats per minute. There was no mean increase in heart rate in the placebo treated patients.

In a placebo-controlled weight management study in patients without T2DM, the percentage of patients who had a change in baseline heart rate of > 20 bpm for 2 or more consecutive visits was 2.4 %, 4.9 % and 6.3 %, for tirzepatide 5 mg, 10 mg and 15 mg, respectively, compared with 1.2 % for placebo. Small mean increases in PR interval were observed with tirzepatide and placebo (mean increase of 0.3 to 1.4 msec and of 0.5 msec respectively). No difference in arrhythmia and cardiac conduction disorder treatment emergent events were observed between tirzepatide 5 mg, 10 mg, 15 mg and placebo (3.7 %, 3.3 %, 3.3 % and 3.6 % respectively).

Injection site reactions

In the placebo-controlled T2DM phase 3 studies, injection site reactions were increased for tirzepatide (3.2 %) compared with placebo (0.4 %).

In 3 placebo-controlled weight management phase 3 studies and in 2 placebo-controlled OSA phase 3 studies, injection site reactions were increased for tirzepatide (8.0 – 8.6 %) compared with placebo (1.8 – 2.6 %).

Overall, in phase 3 studies, the most common signs and symptoms of injection site reactions were erythema and pruritus. The maximum severity of injection site reactions for patients was mild (91 %) or moderate (9 %). No injection site reactions were serious.

Pancreatic enzymes

In the placebo-controlled T2DM phase 3 studies, treatment with tirzepatide resulted in mean increases from baseline in pancreatic amylase of 33 % to 38 % and lipase of 31 % to 42 %. Placebo treated patients had an increase from baseline in amylase of 4 % and no changes were observed in lipase.

In 3 placebo-controlled weight management phase 3 studies and 2 placebo-controlled OSA phase 3 studies, treatment with tirzepatide resulted in mean increases from baseline in pancreatic amylase of 23 – 24.6 % and lipase of 34 - 39 %. Placebo treated patients had an increase from baseline in amylase of 0.7 - 1.8 % and in lipase of 3.5 - 5.7 %.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. Patients may experience gastrointestinal adverse reactions including nausea. There is no specific antidote for overdose of tirzepatide. A prolonged period of

observation and treatment of these symptoms may be necessary, taking into account the half-life of tirzepatide (approximately 5 days).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins, ATC code: A10BX16

Mechanism of action

Tirzepatide is a long acting GIP and GLP-1 receptor agonist, highly selective to human GIP and GLP-1 receptors. Tirzepatide has high affinity to both the GIP and GLP-1 receptors. The activity of tirzepatide on the GIP receptor is similar to native GIP hormone. The activity of tirzepatide on the GLP-1 receptor is lower compared to native GLP-1 hormone. Both receptors are present on the pancreatic α and β endocrine cells, heart, vasculature, immune cells (leukocytes), gut and kidney. GIP receptors are also present on adipocytes.

In addition, both GIP and GLP-1 receptors are expressed in the areas of the brain important to appetite regulation. Animal studies show that tirzepatide distributes to and activates neurons in brain regions involved in regulation of appetite and food intake. Animal studies show that tirzepatide can modulate fat utilization through the GIP receptor. In human adipocytes cultured in vitro, tirzepatide acts on GIP receptors to regulate glucose uptake and modulate lipid uptake and lipolysis.

Glycaemic control

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

Appetite regulation and energy metabolism

Tirzepatide lowers body weight and body fat mass. The body weight reduction is mostly due to reduced fat mass. The mechanisms associated with body weight and body fat mass reduction involve decreased food intake through the regulation of appetite. Clinical studies show that tirzepatide reduces energy intake and appetite by increasing feelings of satiety and fullness, and decreasing feelings of hunger. Tirzepatide also reduces the intensity of food cravings and preferences for high sugar and high fat foods. Tirzepatide modulates fat utilisation.

Pharmacodynamic effects

Insulin secretion

Tirzepatide increases pancreatic β-cell glucose sensitivity. It enhances first- and second-phase insulin secretion in a glucose dependent manner.

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

Insulin sensitivity

Tirzepatide improves insulin sensitivity.

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

Tirzepatide lowers body weight in patients with obesity and overweight, and in patients with type 2 diabetes (irrespective of body weight), which may contribute to improvement in insulin sensitivity.

Glucagon concentration

Tirzepatide reduced the fasting and postprandial glucagon concentrations in a glucose dependent manner. Tirzepatide 15 mg reduced fasting glucagon concentration by 28 % and glucagon AUC after a mixed meal by 43 %, compared with no change for placebo.

Gastric emptying

Tirzepatide delays gastric emptying which may slow post meal glucose absorption and can lead to a beneficial effect on postprandial glycaemia. Tirzepatide induced delay in gastric emptying diminishes over time.

Clinical efficacy and safety

Type 2 diabetes mellitus

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

Across all studies, treatment with tirzepatide demonstrated sustained, statistically significant and clinically meaningful reductions from baseline in HbA1c as the primary objective compared to either placebo or active control treatment (semaglutide, insulin degludec and insulin glargine) for up to 1 year. In 1 study these effects were sustained for up to 2 years. Statistically significant and clinically meaningful reductions from baseline in body weight were also demonstrated. Results from the phase 3 studies are presented below based on the on-treatment data without rescue therapy in the modified intent-to-treat (mITT) population consisting of all randomly assigned patients who were exposed to at least 1 dose of study treatment, excluding patients discontinuing study treatment due to inadvertent enrolment.

SURPASS-1 – Monotherapy

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

Table 2. SURPASS-1: Results at week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
mITT population (n)		121	121	120	113
HbA_{1c} (%)	Baseline (mean)	7.97	7.88	7.88	8.08
	Change from baseline	-1.87##	-1.89##	-2.07##	+0.04
	Difference from placebo [95 % CI]	-1.91** [-2.18, -1.63]	-1.93** [-2.21, -1.65]	-2.11** [-2.39, -1.83]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	63.6	62.6	62.6	64.8
	Change from baseline	-20.4##	-20.7##	-22.7##	+0.4
	Difference from placebo [95 % CI]	-20.8** [-23.9, -17.8]	-21.1** [-24.1, -18.0]	-23.1** [-26.2, -20.0]	-
Patients (%) achieving HbA_{1c}	< 7 %	86.8**	91.5**	87.9**	19.6
	≤ 6.5 %	81.8††	81.4††	86.2††	9.8
	< 5.7 %	33.9**	30.5**	51.7**	0.9
FSG (mmol/L)	Baseline (mean)	8.5	8.5	8.6	8.6
	Change from baseline	-2.4##	-2.6##	-2.7##	+0.7#
	Difference from placebo [95 % CI]	-3.13** [-3.71, -2.56]	-3.26** [-3.84, -2.69]	-3.45** [-4.04, -2.86]	-
FSG (mg/dL)	Baseline (mean)	153.7	152.6	154.6	155.2
	Change from baseline	-43.6##	-45.9##	-49.3##	+12.9#
	Difference from placebo [95 % CI]	-56.5** [-66.8, -46.1]	-58.8** [-69.2, -48.4]	-62.1** [-72.7, -51.5]	-
Body weight (kg)	Baseline (mean)	87.0	85.7	85.9	84.4
	Change from baseline	-7.0##	-7.8##	-9.5##	-0.7
	Difference from placebo [95 % CI]	-6.3** [-7.8, -4.7]	-7.1** [-8.6, -5.5]	-8.8** [-10.3, -7.2]	-
Patients (%) achieving weight loss	≥ 5 %	66.9††	78.0††	76.7††	14.3
	≥ 10 %	30.6††	39.8††	47.4††	0.9
	≥ 15 %	13.2†	17.0†	26.7†	0.0

*p < 0.05, ** p < 0.001 for superiority, adjusted for multiplicity.
†p < 0.05, ††p < 0.001 compared to placebo, not adjusted for multiplicity.
#p < 0.05, ## p < 0.001 compared to baseline, not adjusted for multiplicity.

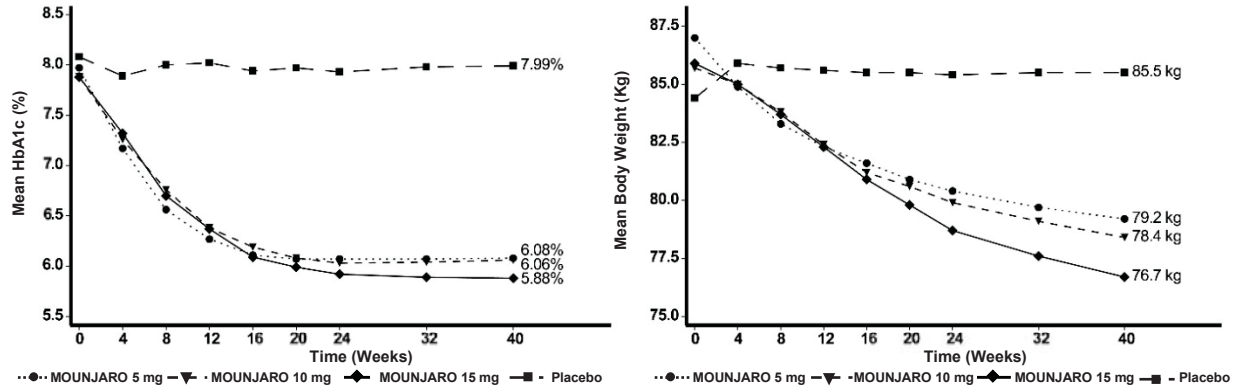

Figure 1. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 40

SURPASS-2 – Combination therapy with metformin

In a 40 week active-controlled open-label study, (double-blind with respect to tirzepatide dose assignment) 1 879 patients were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or

semaglutide 1 mg once weekly, all in combination with metformin. Patients had a mean age of 57 years and 47 % were men. At baseline the patients had a mean duration of diabetes of 9 years and the mean BMI was 34 kg/m^2.

Table 3. SURPASS-2: Results at week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 1 mg
mITT population (n)		470	469	469	468
HbA_{1c} (%)	Baseline (mean)	8.33	8.31	8.25	8.24
	Change from baseline	-2.09$^{\#\#}$	-2.37$^{\#\#}$	-2.46$^{\#\#}$	-1.86$^{\#\#}$
	Difference from semaglutide [95 % CI]	-0.23** [-0.36, -0.10]	-0.51** [-0.64, -0.38]	-0.60** [-0.73, -0.47]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	67.5	67.3	66.7	66.6
	Change from baseline	-22.8$^{\#\#}$	-25.9$^{\#\#}$	-26.9$^{\#\#}$	-20.3$^{\#\#}$
	Difference from semaglutide [95 % CI]	-2.5** [-3.9, -1.1]	-5.6** [-7.0, -4.1]	-6.6** [-8.0, -5.1]	N/A
Patients (%) achieving HbA_{1c}	< 7 %	85.5*	88.9**	92.2**	81.1
	≤ 6.5 %	74.0†	82.1††	87.1††	66.2
	< 5.7 %	29.3††	44.7**	50.9**	19.7
FSG (mmol/L)	Baseline (mean)	9.67	9.69	9.56	9.49
	Change from baseline	-3.11$^{\#\#}$	-3.42$^{\#\#}$	-3.52$^{\#\#}$	-2.70$^{\#\#}$
	Difference from semaglutide [95 % CI]	-0.41† [-0.65, -0.16]	-0.72†† [-0.97, -0.48]	-0.82†† [-1.06, -0.57]	-
FSG (mg/dL)	Baseline (mean)	174.2	174.6	172.3	170.9
	Change from baseline	-56.0$^{\#\#}$	-61.6$^{\#\#}$	-63.4$^{\#\#}$	-48.6$^{\#\#}$
	Difference from semaglutide [95 % CI]	-7.3† [-11.7, -3.0]	-13.0†† [-17.4, -8.6]	-14.7†† [-19.1, -10.3]	-
Body weight (kg)	Baseline (mean)	92.6	94.9	93.9	93.8
	Change from baseline	-7.8$^{\#\#}$	-10.3$^{\#\#}$	-12.4$^{\#\#}$	-6.2$^{\#\#}$
	Difference from semaglutide [95 % CI]	-1.7** [-2.6, -0.7]	-4.1** [-5.0, -3.2]	-6.2** [-7.1, -5.3]	-
Patients (%) achieving weight loss	≥ 5 %	68.6†	82.4††	86.2††	58.4
	≥ 10 %	35.8††	52.9††	64.9††	25.3
	≥ 15 %	15.2†	27.7††	39.9††	8.7

$^{*}p < 0.05$, ** $p < 0.001$ for superiority, adjusted for multiplicity.

$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.001$ compared to semaglutide 1 mg, not adjusted for multiplicity.

$^{\#}p < 0.05$, $^{\#\#}p < 0.001$ compared to baseline, not adjusted for multiplicity.

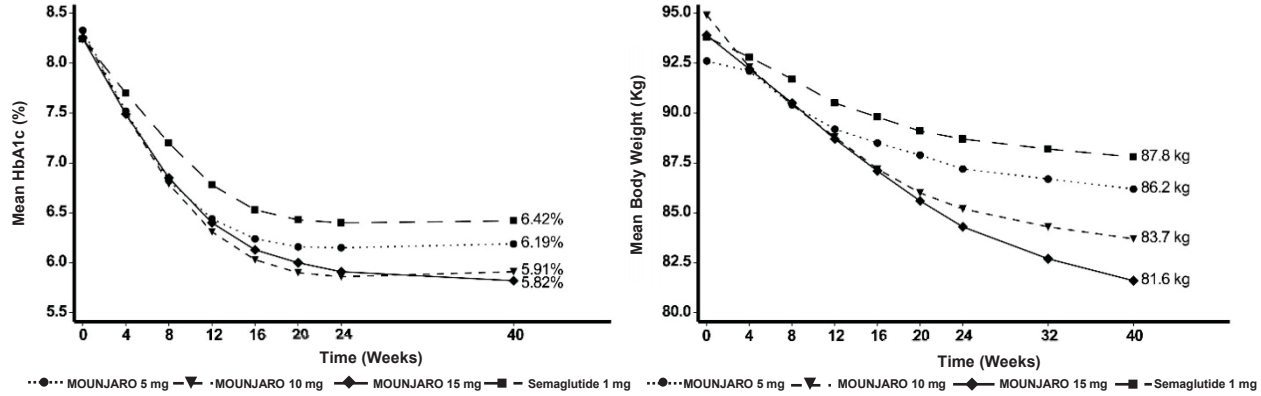

Figure 2. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 40

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

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

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

Table 4. SURPASS-3: Results at week 52

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Titrated insulin degludec
mITT population (n)		358	360	358	359
HbA_{1c} (%)	Baseline (mean)	8.17	8.19	8.21	8.13
	Change from baseline	-1.93##	-2.20##	-2.37##	-1.34##
	Difference from insulin degludec [95 % CI]	-0.59** [-0.73, -0.45]	-0.86** [-1.00, -0.72]	-1.04** [-1.17, -0.90]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	65.8	66.0	66.3	65.4
	Change from baseline	-21.1##	-24.0##	-26.0##	-14.6##
	Difference from insulin degludec [95 % CI]	-6.4** [-7.9, -4.9]	-9.4** [-10.9, -7.9]	-11.3** [-12.8, -9.8]	-
Patients (%) achieving HbA_{1c}	< 7 %	82.4**	89.7**	92.6**	61.3
	≤ 6.5 %	71.4††	80.3††	85.3††	44.4
	< 5.7 %	25.8††	38.6††	48.4††	5.4
FSG (mmol/L)	Baseline (mean)	9.54	9.48	9.35	9.24
	Change from baseline	-2.68##	-3.04##	-3.29##	-3.09##
	Difference from insulin degludec [95 % CI]	0.41† [0.14, 0.69]	0.05 [-0.24, 0.33]	-0.20 [-0.48, 0.08]	-
FSG (mg/dL)	Baseline (mean)	171.8	170.7	168.4	166.4
	Change from baseline	-48.2##	-54.8##	-59.2##	-55.7##
	Difference from insulin degludec [95 % CI]	7.5† [2.4, 12.5]	0.8 [-4.3, 5.9]	-3.6 [-8.7, 1.5]	-
Body weight (kg)	Baseline (mean)	94.5	94.3	94.9	94.2
	Change from baseline	-7.5##	-10.7##	-12.9##	+2.3##
	Difference from insulin degludec [95 % CI]	-9.8** [-10.8, -8.8]	-13.0** [-14.0, -11.9]	-15.2** [-16.2, -14.2]	-
Patients (%) achieving weight loss	≥ 5 %	66.0††	83.7††	87.8††	6.3
	≥ 10 %	37.4††	55.7††	69.4††	2.9
	≥ 15 %	12.5††	28.3††	42.5††	0.0

*p < 0.05, **p < 0.001 for superiority, adjusted for multiplicity.
†p < 0.05, ††p < 0.001 compared to insulin degludec, not adjusted for multiplicity.
#p < 0.05, ## p < 0.001 compared to baseline, not adjusted for multiplicity.

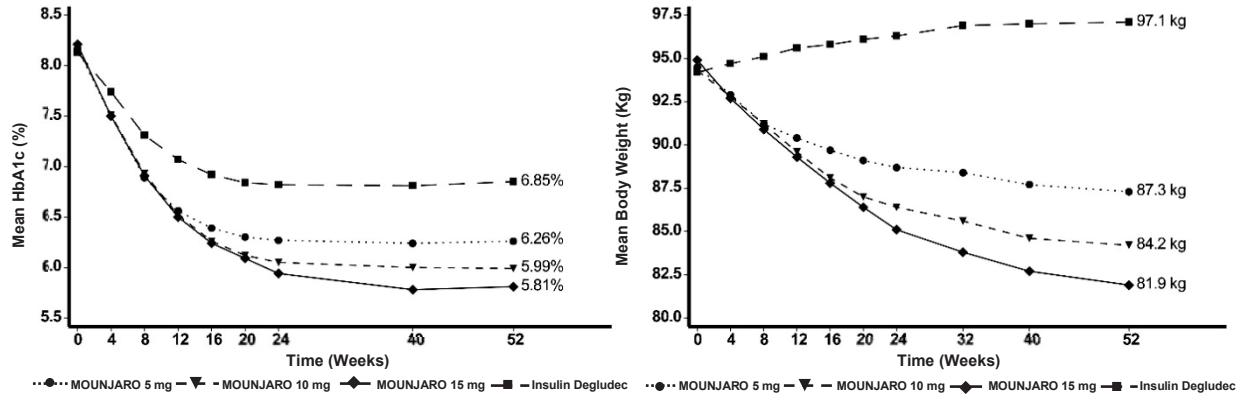

Figure 3. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 52

Continuous glucose monitoring (CGM)
A subset of patients (N = 243) participated in an evaluation of the 24 hour glucose profiles captured with blinded CGM. At 52 weeks, patients treated with tirzepatide (10 mg and 15 mg pooled) spent significantly more time with glucose values in the euglycaemic range defined as 71 to 140 mg/dL (3.9

to 7.8 mmol/L) compared to patients treated with insulin degludec, with 73 % and 48 % of the 24 hour period in range, respectively.

SURPASS-4 – Combination therapy with 1-3 oral antidiabetic medicinal products: metformin, sulphonylureas or SGLT2i

In an active-controlled open-label study of up to 104 weeks (primary endpoint at 52 weeks), 2 002 patients with type 2 diabetes and increased cardiovascular risk were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or insulin glargine once daily on a background of metformin (95 %) and/or sulphonylureas (54 %) and/or SGLT2i (25 %). At baseline the patients had a mean duration of diabetes of 12 years, a mean BMI of 33 kg/m^2, a mean age of 64 years and 63 % were men. Patients treated with insulin glargine started at a dose of 10 U/day which was adjusted using an algorithm with a fasting blood glucose target of < 5.6 mmol/L. The mean dose of insulin glargine at week 52 was 44 units/day.

Table 5. SURPASS-4: Results at week 52

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Titrated insulin glargine
mITT population (n)		328	326	337	998
52 weeks					
HbA_{1c} (%)	Baseline (mean)	8.52	8.60	8.52	8.51
	Change from baseline	-2.24$^{\#\#}$	-2.43$^{\#\#}$	-2.58$^{\#\#}$	-1.44$^{\#\#}$
	Difference from insulin glargine [95 % CI]	-0.80** [-0.92, -0.68]	-0.99** [-1.11, -0.87]	-1.14** [-1.26, -1.02]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	69.6	70.5	69.6	69.5
	Change from baseline	-24.5$^{\#\#}$	-26.6$^{\#\#}$	-28.2$^{\#\#}$	-15.7$^{\#\#}$
	Difference from insulin glargine [95 % CI]	-8.8** [-10.1, -7.4]	-10.9** [-12.3, -9.6]	-12.5** [-13.8, -11.2]	-
Patients (%) achieving HbA_{1c}	< 7 %	81.0**	88.2**	90.7**	50.7
	≤ 6.5 %	66.0††	76.0††	81.1††	31.7
	< 5.7 %	23.0††	32.7††	43.1††	3.4
FSG (mmol/L)	Baseline (mean)	9.57	9.75	9.67	9.37
	Change from baseline	-2.80$^{\#\#}$	-3.06$^{\#\#}$	-3.29$^{\#\#}$	-2.84$^{\#\#}$
	Difference from insulin glargine [95 % CI]	0.04 [-0.22, 0.30]	-0.21 [-0.48, 0.05]	-0.44†† [-0.71, -0.18]	-
FSG (mg/dL)	Baseline (mean)	172.3	175.7	174.2	168.7
	Change from baseline	-50.4$^{\#\#}$	-54.9$^{\#\#}$	-59.3$^{\#\#}$	-51.4$^{\#\#}$
	Difference from insulin glargine [95 % CI]	1.0 [-3.7, 5.7]	-3.6 [-8.2, 1.1]	-8.0†† [-12.6, -3.4]	-
Body weight (kg)	Baseline (mean)	90.3	90.7	90.0	90.3
	Change from baseline	-7.1$^{\#\#}$	-9.5$^{\#\#}$	-11.7$^{\#\#}$	+1.9$^{\#\#}$
	Difference from insulin glargine [95 % CI]	-9.0** [-9.8, -8.3]	-11.4** [-12.1, -10.6]	-13.5** [-14.3, -12.8]	-
Patients (%) achieving weight loss	≥ 5 %	62.9††	77.6††	85.3††	8.0
	≥ 10 %	35.9††	53.0††	65.6††	1.5
	≥ 15 %	13.8††	24.0††	36.5††	0.5

* $p < 0.05$, ** $p < 0.001$ for superiority, adjusted for multiplicity.

$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.001$ compared to insulin glargine, not adjusted for multiplicity.

$^{\#}p < 0.05$, $^{\#\#}p < 0.001$ compared to baseline, not adjusted for multiplicity.

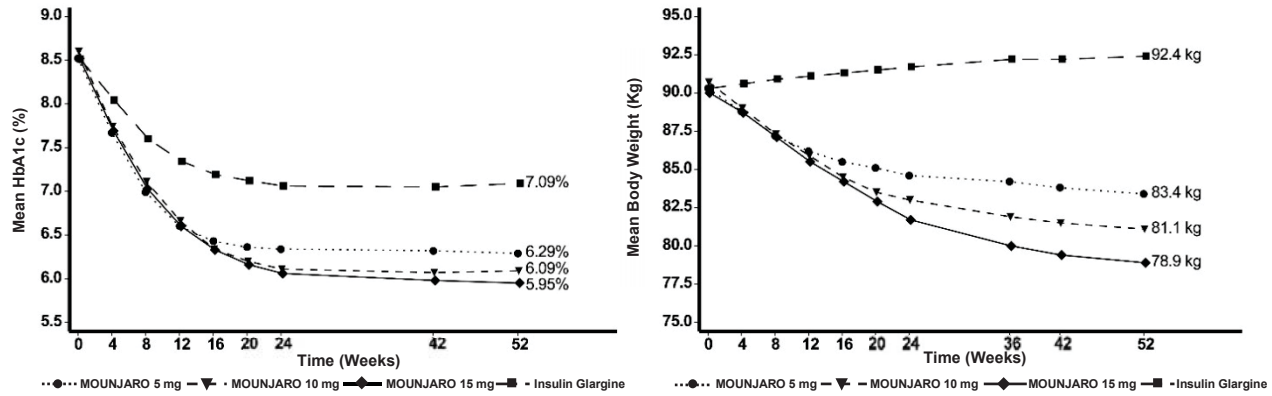

Figure 4. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 52

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

In a 40 week double-blind placebo-controlled study, 475 patients with inadequate glycaemic control using insulin glargine with or without metformin were randomised to tirzepatide 5 mg, 10 mg or

15 mg once weekly or placebo. Insulin glargine doses were adjusted utilizing an algorithm with a fasting blood glucose target of < 5.6 mmol/L. At baseline the patients had a mean duration of diabetes of 13 years, a mean BMI of 33 kg/m^2, a mean age of 61 years and 56 % were men. The overall estimated median dose of insulin glargine at baseline was 34 units/day. The median dose of insulin glargine at week 40 was 38, 36, 29 and 59 units/day for tirzepatide 5 mg, 10 mg, 15 mg and placebo respectively.

Table 6. SURPASS-5: Results at week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
mITT population (n)		116	118	118	119
HbA_{1c} (%)	Baseline (mean)	8.29	8.34	8.22	8.39
	Change from baseline	-2.23$^{\#\#}$	-2.59$^{\#\#}$	-2.59$^{\#\#}$	-0.93$^{\#\#}$
	Difference from placebo [95 % CI]	-1.30** [-1.52, -1.07]	-1.66** [-1.88, -1.43]	-1.65** [-1.88, -1.43]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	67.1	67.7	66.4	68.2
	Change from baseline	-24.4$^{\#\#}$	-28.3$^{\#\#}$	-28.3$^{\#\#}$	-10.2$^{\#\#}$
	Difference from placebo [95 % CI]	-14.2** [-16.6, -11.7]	-18.1** [-20.6, -15.7]	-18.1** [-20.5, -15.6]	-
Patients (%) achieving HbA_{1c}	< 7 %	93.0**	97.4**	94.0**	33.9
	≤ 6.5 %	80.0††	94.7††	92.3††	17.0
	< 5.7 %	26.1††	47.8††	62.4††	2.5
FSG (mmol/L)	Baseline (mean)	9.00	9.04	8.91	9.13
	Change from baseline	-3.41$^{\#\#}$	-3.77$^{\#\#}$	-3.76$^{\#\#}$	-2.16$^{\#\#}$
	Difference from placebo [95 % CI]	-1.25** [-1.64, -0.86]	-1.61** [-2.00, -1.22]	-1.60** [-1.99, -1.20]	-
FSG (mg/dL)	Baseline (mean)	162.2	162.9	160.4	164.4
	Change from baseline	-61.4$^{\#\#}$	-67.9$^{\#\#}$	-67.7$^{\#\#}$	-38.9$^{\#\#}$
	Difference from placebo [95 % CI]	-22.5** [-29.5, -15.4]	-29.0** [-36.0, -22.0]	-28.8** [-35.9, -21.6]	-
Body weight (kg)	Baseline (mean)	95.5	95.4	96.2	94.1
	Change from baseline	-6.2$^{\#\#}$	-8.2$^{\#\#}$	-10.9$^{\#\#}$	+1.7$^{\#}$
	Difference from placebo [95 % CI]	-7.8** [-9.4, -6.3]	-9.9** [-11.5, -8.3]	-12.6** [-14.2, -11.0]	-
Patients (%) achieving weight loss	≥ 5 %	53.9††	64.6††	84.6††	5.9
	≥ 10 %	22.6††	46.9††	51.3††	0.9
	≥ 15 %	7.0†	26.6†	31.6††	0.0

$^{*}p < 0.05$, ** $p < 0.001$ for superiority, adjusted for multiplicity.

$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.001$ compared to placebo, not adjusted for multiplicity.

$^{\#}p < 0.05$, $^{\#\#}p < 0.001$ compared to baseline, not adjusted for multiplicity.

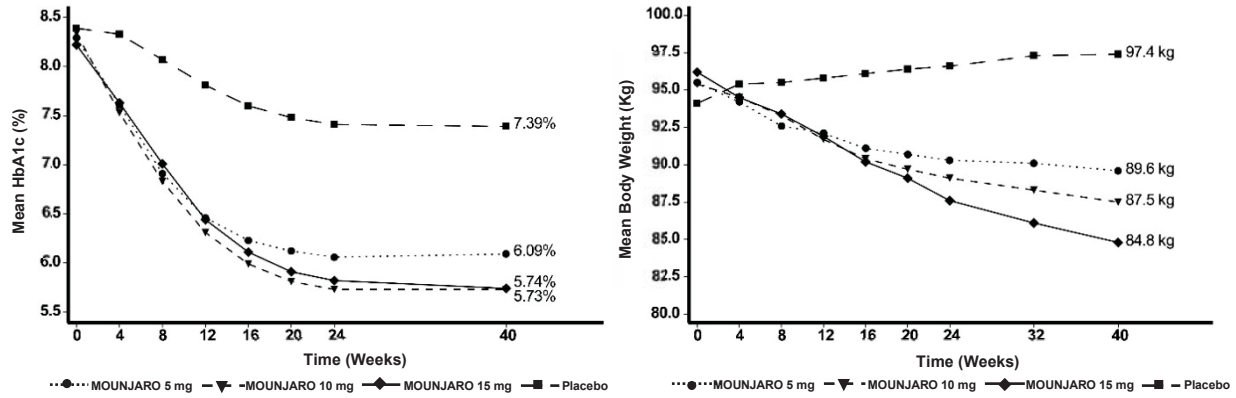

Figure 5. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 40

Weight management

The efficacy and safety of tirzepatide for weight management, in combination with a reduced calorie intake and increased physical activity, in patients with obesity (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight-related comorbidity (such as treated or untreated dyslipidaemia, hypertension, obstructive sleep apnoea, or cardiovascular disease), and with prediabetes or normoglycemia, but without type 2 diabetes mellitus, were evaluated in three randomised double-blinded, placebo-controlled phase 3 studies (SURMOUNT-1, SURMOUNT-3, SURMOUNT-4). A total of 3 900 adult patients (2 518 randomised to tirzepatide) were included in these studies.

Treatment with tirzepatide demonstrated clinically meaningful and sustained weight reduction compared with placebo. Furthermore, a higher percentage of patients achieved ≥ 5 %, ≥ 10 %, ≥ 15 % and ≥ 20 % weight loss with tirzepatide compared with placebo.

The efficacy and safety of tirzepatide for weight management in patients with type 2 diabetes were evaluated in a randomised double-blinded, placebo-controlled phase 3 study (SURMOUNT-2), and in a subpopulation of patients with BMI ≥ 27 kg/m^2 in five randomised phase 3 studies (SURPASS-1 to -5). A total of 6 330 patients with BMI ≥ 27 kg/m^2 (4 249 randomised to treatment with tirzepatide) were included in these studies. In SURMOUNT-2 treatment with tirzepatide demonstrated clinically meaningful and sustained weight reduction compared with placebo. Furthermore, a higher percentage of patients achieved ≥ 5 %, ≥ 10 %, ≥ 15 % and ≥ 20 % weight loss with tirzepatide compared with placebo. Subgroup analyses of patients with obesity or overweight in the SURPASS studies (amounting to 86 % of the overall SURPASS-1 to -5 population) showed sustained weight reduction, and a higher percentage of patients achieving weight reduction targets compared to active comparator/placebo.

In all SURMOUNT studies, the same tirzepatide dose escalation scheme was used as in the SURPASS programme (starting with 2.5 mg for 4 weeks, followed by increases in 2.5 mg increments every 4 weeks until the assigned dose was reached).

SURMOUNT-1

In a 72 week double-blind placebo-controlled study, 2 539 adult patients with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight-related comorbid condition, were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or placebo. All patients were counselled on a reduced-calorie diet and increased physical activity throughout the trial. At baseline, patients had a mean age of 45 years, 67.5 % were women and 40.6 % of patients had prediabetes. Mean BMI at baseline was 38 kg/m^2.

Table 7. SURMOUNT-1: Results at week 72

	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
mITT population (n)	630	636	630	643
Body weight				
Baseline (kg)	102.9	105.9	105.5	104.8
Change (%) from baseline	-16.0††	-21.4††	-22.5††	-2.4
Difference (%) from placebo [95 % CI]	-13.5** [-14.6, -12.5]	-18.9** [-20.0, -17.8]	-20.1** [-21.2, -19.0]	-
Change (kg) from baseline	-16.1††	-22.2††	-23.6††	-2.4††
Difference (kg) from placebo [95 % CI]	-13.8## [-15.0, -12.6]	-19.8## [-21.0, -18.6]	-21.2## [-22.4, -20.0]	-
Patients (%) achieving body weight reduction				
≥ 5 %	89.4**	96.2**	96.3**	27.9
≥ 10 %	73.4##	85.9**	90.1**	13.5
≥ 15 %	50.2##	73.6**	78.2**	6.0
≥ 20 %	31.6##	55.5**	62.9**	1.3
Waist circumference (cm)				
Baseline	113.2	114.9	114.4	114.0
Change from baseline	-14.6††	-19.4††	-19.9††	-3.4††
Difference from placebo [95 % CI]	-11.2## [-12.3, -10.0]	-16.0** [-17.2, -14.9]	-16.5** [-17.7, -15.4]	-

††p < 0.001 versus baseline.
**p < 0.001 versus placebo, adjusted for multiplicity.
##p < 0.001 versus placebo, not adjusted for multiplicity.

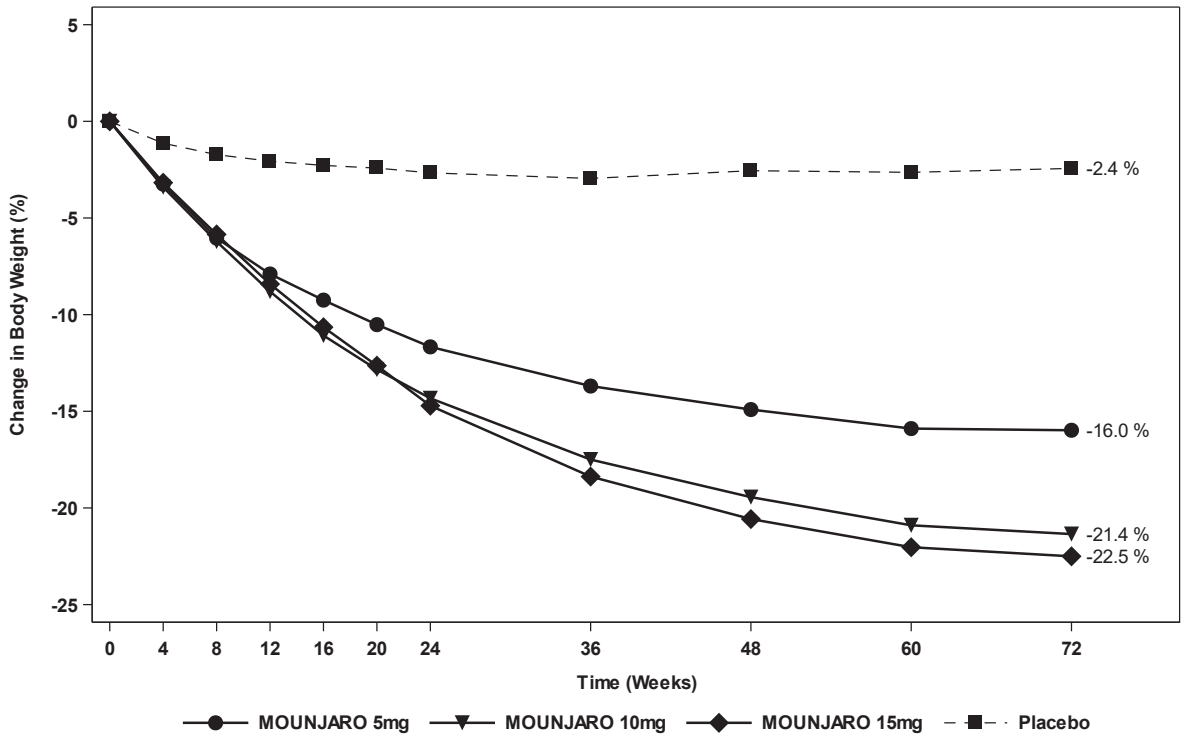

Figure 6. Mean change in body weight (%) from baseline to week 72

In SURMOUNT-1, pooled doses of tirzepatide 5 mg, 10 mg, and 15 mg led to a significant improvement compared to placebo in systolic blood pressure (-8.1 mmHg vs. -1.3 mmHg), triglycerides (-27.6 % vs. -6.3 %), non-HDL-C (-11.3 % vs. -1.8 %), HDL-C (7.9 % vs. 0.3 %), and fasting insulin (-46.9 % vs. -9.7 %).

Among the patients in SURMOUNT-1 with prediabetes at baseline (N = 1032), 95.3 % patients treated with tirzepatide reverted to normoglycemia at week 72, as compared with 61.9 % of patients in the placebo group.

SURMOUNT-2

In a 72 week double-blind placebo-controlled study, 938 adult patients with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and type 2 diabetes, were randomised to tirzepatide 10 mg or 15 mg once weekly or placebo. Patients included in the trial had HbA1c 7-10 % and were treated with either diet and exercise alone, or with one or more oral anti-hyperglycemic agent . All patients were counselled on a reduced calorie diet and increased physical activity throughout the trial. Patients had a mean age of 54 years and 51 % were women.Mean BMI at baseline was 36.1 kg/m^2.

Table 8. SURMOUNT-2: Results at week 72

	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
mITT population (n)	312	311	315
Body weight			
Baseline (kg)	101.1	99.5	101.7
Change (%) from baseline	-13.4††	-15.7††	-3.3††
Difference (%) from placebo [95 % CI]	-10.1** [-11.5, -8.8]	-12.4** [-13.7, -11.0]	-
Change (kg) from baseline	-13.5††	-15.6††	-3.2
Difference (kg) from placebo [95 % CI]	-10.3## [-11.7, -8.8]	-12.4## [-13.8,-11.0]	-
Patients (%) achieving body weight reduction			
≥ 5 %	81.6**	86.4**	30.5
≥ 10 %	63.4**	69.6**	8.7
≥ 15 %	41.4**	51.8**	2.6
≥ 20 %	23.0**	34.0**	1.0
Waist circumference (cm)			
Baseline	114.3	114.6	116.1
Change from baseline	-11.2††	-13.8††	-3.4††
Difference from placebo [95 % CI]	-7.8** [-9.2, -6.4]	-10.4** [-11.8, -8.9]	-
HbA_{1c} (mmol/mol)			
Baseline	64.1	64.7	63.4
Change from baseline	-23.4††	-24.3††	-1.8†
Difference from placebo [95 % CI]	-21.6** [-23.5, -19.6]	-22.5** [-24.4, -20.6]	-
HbA_{1c} (%)			
Baseline	8.0	8.1	8.0
Change from baseline	-2.1††	-2.2††	-0.2†
Difference from placebo [95 % CI]	-2.0** [-2.2, -1.8]	-2.1** [-2.2, -1.9]	-
Patients (%) achieving HbA1c			
< 7 %	90.0**	90.7**	29.3
≤ 6.5 %	84.1**	86.7**	15.5
< 5.7 %	50.2**	55.3**	2.8
FSG (mmol/L)			
Baseline	8.8	9.0	8.7
Change from baseline	-2.7††	-2.9††	-0.1
Difference from placebo [95 % CI]	-2.6** [-2.9, -2.3]	-2.7** [-3.1, -2.4]	-
FSG (mg/dL)			
Baseline	157.8	161.5	156.7
Change from baseline	-49.2††	-51.7††	-2.4
Difference from placebo [95 % CI]	-46.8** [-52.7, -40.9]	-49.3** [-55.2, -43.3]	-

†p< 0.05 versus baseline
††p < 0.001 versus baseline.
**p < 0.001 versus placebo, adjusted for multiplicity.
##p < 0.001 versus placebo, not adjusted for multiplicity.

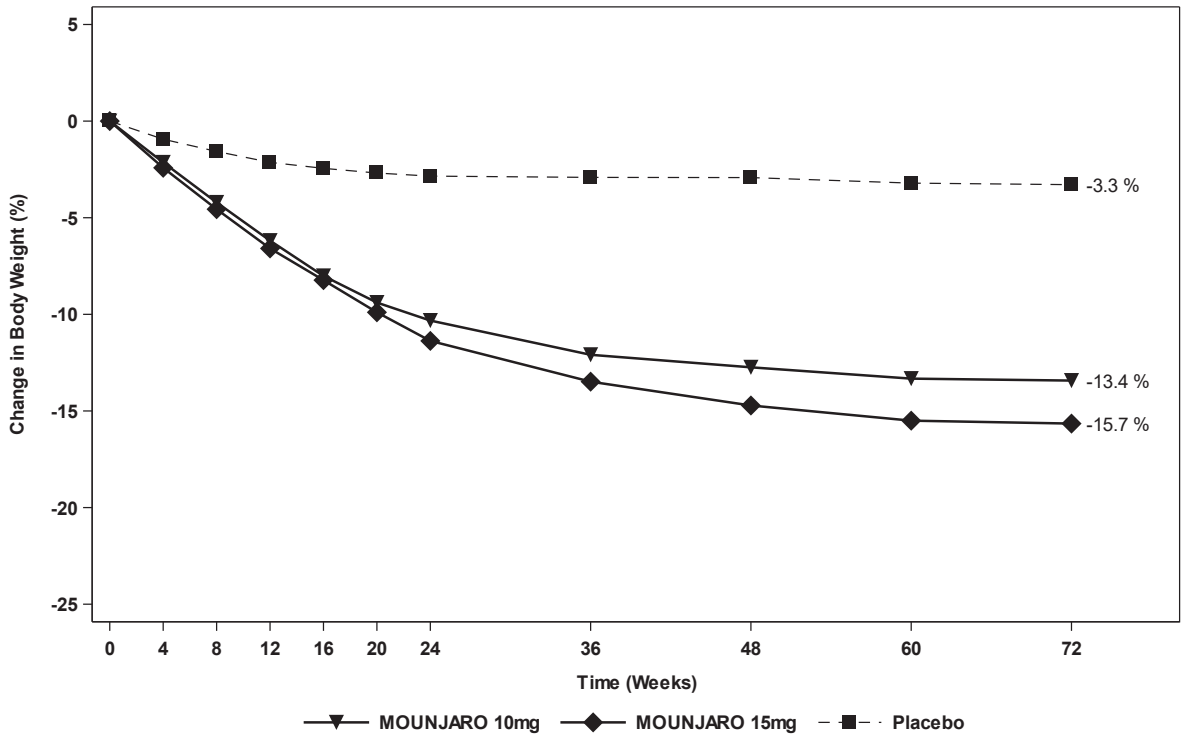

Figure 7. Mean change in body weight (%) from baseline to week 72

In SURMOUNT-2, pooled doses of tirzepatide 10 mg and 15 mg led to a significant improvement compared to placebo in systolic blood pressure (-7.2 mmHg vs. -1.0 mmHg), triglycerides (-28.6 % vs. -5.8 %), non-HDL-C (-6.6 % vs. 2.3 %), and HDL-C (8.2 % vs. 1.1 %).

SURMOUNT-3

In an 84 week study, 806 adult patients with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight related comorbid condition, entered a 12 week intensive lifestyle intervention lead-in period consisting of a low calorie diet (1 200-1 500 kcal/day), increased physical activity and frequent behavioural counselling. At the end of the 12 week lead-in period, 579 patients who achieved ≥ 5.0 % weight reduction were randomised to tirzepatide maximum tolerated dose (MTD) of 10 mg or 15 mg once weekly or to placebo, for 72 weeks (double-blind phase). Patients were on a reduced-calorie diet and increased physical activity throughout the double-blind phase of the study. At randomisation patients had a mean age of 46 years and 63 % were women. Mean BMI at randomisation was 35.9 kg/m^2.

Table 9. SURMOUNT-3: Results at week 72

	Tirzepatide MTD	Placebo
mITT population (n)	287	292
Body weight		
Baseline[1] (kg)	102.3	101.3
Change (%) from baseline[1]	-21.1[††]	3.3[††]
Difference (%) from placebo [95 % CI]	-24.5[**] [-26.1, -22.8]	-
Change (kg) from baseline[1]	-21.5[††]	3.5[††]
Difference (kg) from placebo [95 % CI]	-25.0[##] [-26.9, -23.2]	-
Patients (%) achieving body weight reduction		
≥ 5 %	94.4[**]	10.7
≥ 10 %	88.0[**]	4.8
≥ 15 %	73.9[**]	2.1
≥ 20 %	54.9[**]	1.0
Patients (%) who maintain ≥80% of the body weight lost during the 12-week lead-in period	98.6[**]	37.8
Waist circumference (cm)		
Baseline[1]	109.2	109.6
Change from baseline[1]	-16.8[††]	1.1
Difference from placebo [95 % CI]	-17.9[**] [-19.5, -16.3]	-

[1]Randomisation (Week 0)
[††]$p < 0.001$ versus baseline[1].
[**]$p < 0.001$ versus placebo, adjusted for multiplicity.
[##]$p < 0.001$ versus placebo, not adjusted for multiplicity.

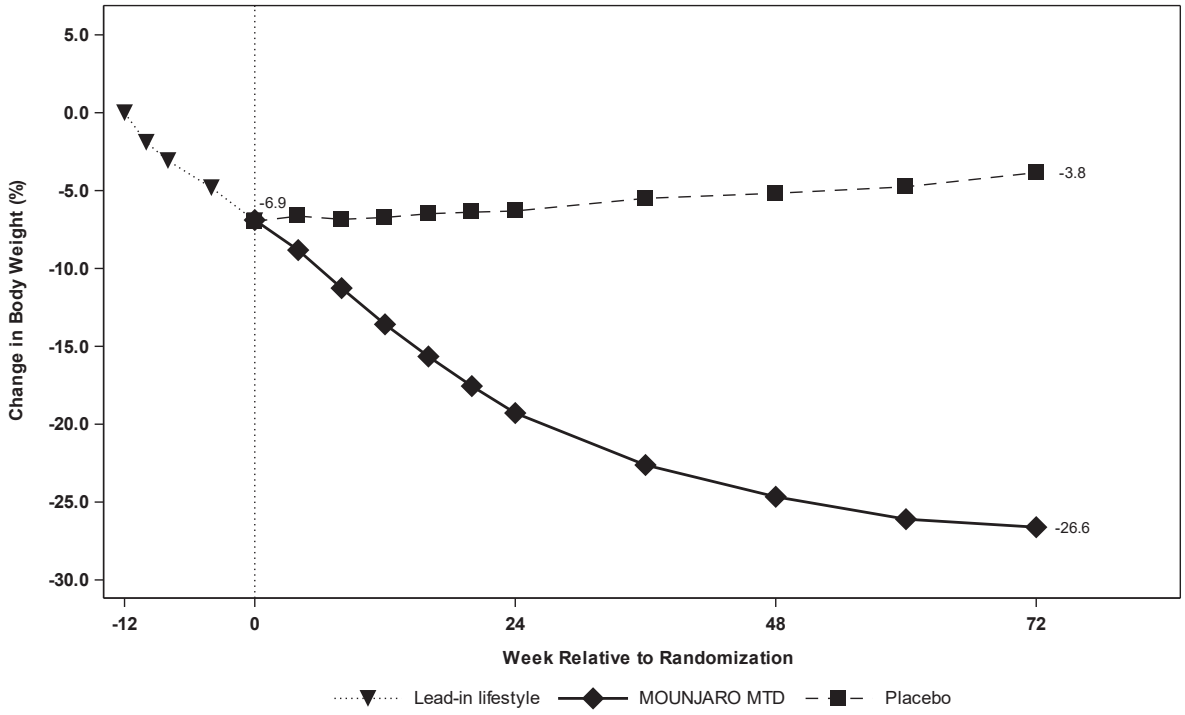

Figure 8. Mean change in body weight (%) from Week -12 to week 72

SURMOUNT-4

In an 88 week study, 783 adult patients with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight related comorbid condition, were enrolled in a 36 week open label tirzepatide lead-in phase. At the start of lead-in period, the enrolled patients had a mean body weight of 107.0 kg and a mean BMI of 38.3 kg/m^2. At the end of the lead-in period, 670 patients who achieved tirzepatide MTD of 10 mg or 15 mg dose were randomised to continue treatment with tirzepatide once weekly or to switch to placebo for 52 weeks (double-blind phase). Patients were counselled on a reduced calorie diet and increased physical activity throughout the trial. At randomisation (week 36), patients had a mean age of 49 years and 71 % were women. Mean body weight at randomisation was 85.2 kg and mean BMI was 30.5 kg/m^2.

Patients who continued treatment with tirzepatide for an additional 52 weeks (up to 88 weeks in total) maintained and experienced further weigh loss after the initial weight reduction achieved during the 36 week lead-in phase. The weight reduction was superior and clinically meaningful compared to the placebo group, in which a substantial regain of body weight lost during the lead-in phase was observed (see Table 10 and Figure 9). Nevertheless, the observed mean body weight for placebo-treated patients was lower at week 88 than at the start of the lead-in phase (see Figure 9).

Table 10. SURMOUNT-4: Results at week 88

	Tirzepatide MTD	**Placebo**
mITT population (n) only patients at Week 36	335	335
Body weight		
Weight (kg) at Week 0 (baseline)	106.7	107.8
Weight (kg) at Week 36 (randomisation)	84.5	85.9
Change (%) from Week 36 at Week 88	-6.7††	14.8††
Difference (%) from placebo at Week 88 [95 % CI]	-21.4** [-22.9, -20.0]	-
Change (kg) from Week 36 at Week 88	-5.7††	11.9††
Difference (kg) from placebo at Week 88 [95 % CI]	-17.6## [-18.8, -16.4]	-
Patients (%) achieving body weight reduction from Week 0 to Week 88		
≥ 5 %	98.5**	69.0
≥ 10 %	94.0**	44.4
≥ 15 %	87. 1**	24.0
≥ 20 %	72.6**	11.6
Patients (%) who maintain ≥80% of the body weight lost during the 36-week lead-in period at Week 88	93.4**	13.5
Waist circumference (cm)		
Baseline (Week 0)	114.9	115.6
Randomisation (Week 36)	96.7	98.2
Change from randomisation (Week 36)	-4.6††	8.3††
Difference from placebo [95 % CI]	-12.9** [-14.1, -11.7]	-

††p < 0.001 versus baseline.
**p < 0.001 versus placebo, adjusted for multiplicity.
##p < 0.001 versus placebo, not adjusted for multiplicity.

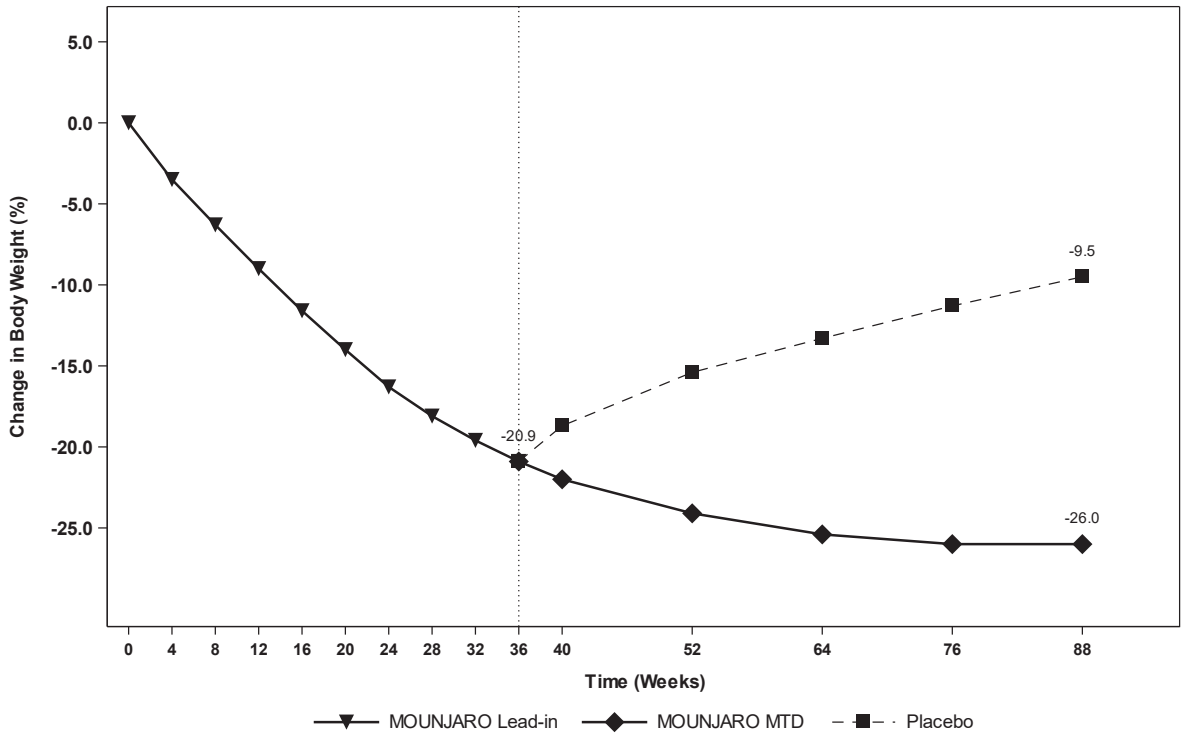

Figure 9. Mean change in body weight (%) from baseline (Week 0) to week 88

Risk of weight regain to > 95 % of study baseline (Week 0) weight at week 88
Time to event analysis showed that continued tirzepatide treatment during the double-blind period reduced the risk of returning to greater than 95 % body weight observed at Week 0, for those who had already lost at least 5 % since week 0 by approximately 99 % compared with placebo (hazard ratio, 0.013 [95 % CI, 0.004 to 0.046]; $p < 0.001$).

Effect on body composition

Changes in body composition were evaluated in a sub-study in SURMOUNT-1 using dual energy X-ray absorptiometry (DEXA). The results of the DEXA assessment showed that treatment with tirzepatide was accompanied by greater reduction in fat mass than in lean body mass leading to an improvement in body composition compared to placebo after 72 weeks. Furthermore, this reduction in total fat mass was accompanied by a reduction in visceral fat. These results suggest that most of the total weight loss was attributable to a reduction in fat tissue, including visceral fat.

Improvement in physical functioning

Patients with obesity or overweight without diabetes who received tirzepatide showed small improvements in health-related quality of life, including physical functioning. The improvements were greater in the tirzepatide-treated patients than in those who received placebo. Health-related quality of life was assessed using the generic questionnaire Short Form-36v2 Health Survey Acute, Version (SF-36v2).

Obstructive sleep apnoea

The efficacy and safety of tirzepatide for the treatment of moderate to severe (AHI>15) obstructive sleep apnoea (OSA), in combination with diet and exercise, in patients with obesity were evaluated in two randomized double-blinded, placebo-controlled phase 3 studies (SURMOUNT-OSA Study 1 and Study 2). A total of 469 adult patients with moderate to severe OSA and obesity (234 randomised to treatment with tirzepatide) were included in these studies. Patients with T2DM were excluded. Study 1

enrolled patients unable or unwilling to use Positive Airway Pressure (PAP) therapy. Study 2 enrolled patients on PAP therapy. Study 2 does not allow any conclusion about a potentially added benefit of tirzepatide on top of PAP therapy, since PAP use was suspended 7 days prior to endpoint measurement. All patients were treated with the maximum tolerated dose (MTD; 10 mg or 15 mg) of tirzepatide or placebo, once weekly for 52 weeks.

In both studies, treatment with tirzepatide demonstrated statistically significant and clinically meaningful reduction in the apnoea-hypopnoea index (AHI) compared with placebo (see Table 11). Among tirzepatide treated patients, greater proportion of patients achieved at least 50 % AHI reduction compared to placebo.

SURMOUNT-OSA, Study 1 and Study 2

In two 52 week double-blind placebo-controlled studies, 469 adult patients with moderate to severe OSA and obesity, were randomised to tirzepatide MTD of 10 mg or 15 mg once weekly, or to placebo, once weekly. In Study 1 patients had a mean age of 48 years, 33 % were female, 35 % had moderate OSA, 63 % had severe OSA, 65 % had pre-diabetes, 76 % had hypertension, 10 % had cardiac disorders, and 81 % had dyslipidemia. Patients had a mean Epworth Sleepiness Scale (ESS) of 10.5. In Study 2 patients had a mean age of 52 years, 28 % were female, 31 % had moderate OSA, 68 % had severe OSA, 57 % had pre-diabetes, 77 % had hypertension, 11 % had cardiac disorders, and 84 % had dyslipidemia. Patients had a mean ESS of 10.0.

Table 11. SURMOUNT-OSA, Study 1 and Study 2: Results at week 52

	OSA Study 1		**OSA Study 2**	
	Tirzepatide MTD	**Placebo**	**Tirzepatide MTD**	**Placebo**
mITT population (n)	114	120	119	114
AHI (events/hr)				
Baseline mean	54.3	50.9	45.8	53.1
Change from baseline	-27.4††	-4.8†	-30.4††	-6.0†
Difference from placebo [95 % CI]	-22.5** [-28.7, -16.4]	-	-24.4** [-30.3, -18.6]	-
% Change in AHI				
% Change from baseline	-55.0††	-5.0	-62.8††	-6.4
% Difference from placebo [95% CI]	-49.9** [-62.8, -37.0]	-	-56.4** [-70.7, -42.2]	-
Patients (%) achieving reduction in AHI				
≥50%	62.3	19.2	74.3	22.9
% Difference from placebo [95% CI]	43.6** [31.1, 56.2]	-	50.8** [38.6, 62.9]	-
Sleep apnoea-specific hypoxic burden (% min/h)[a]				
Baseline geometric mean	156.6	148.2	129.9	139.1
Change from baseline	-103.1††	-21.1	-103.0††	-40.7†
Difference from placebo [95% CI]	-82.0** [-107.0, -57.1]	-	-62.4** [-87.1, -37.6]	-
Body weight (kg)				
Baseline mean	117.0	112.7	115.8	115.0
% Change from baseline	-18.1††	-1.3	-20.1††	-2.3†
% Difference from placebo [95% CI]	-16.8** [-18.8, -14.7]	-	-17.8** [-19.9, -15.7]	-

Systolic Blood Pressure (mmHg) [b]				
Baseline mean	128.2	130.3	130.7	130.5
Change from baseline	-9.6††	-1.7	-7.6††	-3.3†
Difference from placebo [95% CI]	-7.9** [-11.0, -4.9]	-	-4.3* [-7.3, -1.2]	-
hsCRP (mg/L) [a]				
Baseline geometric mean	3.6	3.8	3.0	2.7
Change from baseline	-1.6††	-0.8†	-1.4††	-0.3
Difference from placebo [95% CI]	-0.8* [-1.4, -0.3]	-	-1.1** [-1.7, -0.5]	-

† $p < 0.05$, †† $p < 0.001$ versus baseline.
* $p < 0.05$, ** $p < 0.001$ versus placebo, adjusted for multiplicity.
[a] Analysed using log transformed data.
[b] Blood pressure was assessed at Week 48 because PAP withdrawal at Week 52 may confound blood pressure assessment.

Cardiovascular evaluation

Cardiovascular (CV) risk was assessed via a meta-analysis of patients with at least one adjudication confirmed major adverse cardiovascular event (MACE). The composite endpoint of MACE-4 included CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina.

In a primary meta-analysis of phase 2 and 3 registration studies in patients with type 2 diabetes, a total of 116 patients (tirzepatide: 60 [n = 4 410]; all comparators: 56 [n = 2 169]) experienced at least one adjudication confirmed MACE-4: The results showed that tirzepatide was not associated with excess risk for CV events compared with pooled comparators (HR: 0.81; CI: 0.52 to 1.26).

An additional analysis was conducted specifically for the SURPASS-4 study that enrolled patients with established CV disease. A total of 109 patients (tirzepatide: 47 [n = 995]; insulin glargine: 62 [n = 1 000]) experienced at least one adjudication confirmed MACE-4: The results showed that tirzepatide was not associated with excess risk for CV events compared with insulin glargine (HR: 0.74; CI: 0.51 to 1.08).

In 3 placebo-controlled weight management phase 3 studies (SURMOUNT 1-3), a total of 27 participants experienced at least one adjudication confirmed MACE (TZP: 17 (n = 2 806); placebo: 10 (n = 1 250)); the event rate was similar across placebo and tirzepatide.

Blood pressure
In the placebo-controlled phase 3 studies in patients with T2DM, treatment with tirzepatide resulted in a mean decrease in systolic and diastolic blood pressure of 6 to 9 mmHg and 3 to 4 mmHg, respectively. There was a mean decrease in systolic and diastolic blood pressure of 2 mmHg each in placebo treated patients.

In 3 placebo-controlled weight management phase 3 studies (SURMOUNT 1-3), treatment with tirzepatide resulted in a mean decrease in systolic and diastolic blood pressure of 7 mmHg and 4 mmHg, respectively. There was a mean decrease in systolic and diastolic blood pressure of < 1 mmHg each in placebo treated patients.

In two placebo-controlled OSA phase 3 studies with pooled safety analysis, treatment with tirzepatide resulted in a mean decrease in systolic and diastolic blood pressure of 9.0 mmHg and 3.8 mmHg, respectively, at Week 52. There was a mean decrease in systolic and diastolic blood pressure of 2.5 mmHg and 1.0 mmHg, respectively, in placebo treated patients at Week 52.

Other information

Fasting serum glucose

Across SURPASS-1 to -5 trials, treatment with tirzepatide resulted in significant reductions from baseline in FSG (changes from baseline to primary end point were -2.4 mmol/L to -3.8 mmol/L). Significant reductions from baseline in FSG could be observed as early as 2 weeks. Further improvement in FSG was seen through to 42 weeks then was sustained through the longest study duration of 104 weeks.

Postprandial glucose

Across SURPASS-1 to -5 trials, treatment with tirzepatide resulted in significant reductions in mean 2 hour post prandial glucose (mean of 3 main meals of the day) from baseline (changes from baseline to primary end point were -3.35 mmol/L to -4.85 mmol/L).

Triglycerides

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

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

In the 72 week placebo-controlled phase 3 study in patients with obesity or overweight without T2DM (SURMOUNT-1), treatment with tirzepatide 5 mg, 10 mg, and 15 mg resulted in 24 %, 27 % and 31 % reduction in serum triglyceride levels respectively compared to 6 % reduction with placebo.

In the 72 week placebo-controlled phase 3 study in patients with obesity or overweight with T2DM (SURMOUNT-2), treatment with tirzepatide 10 mg and 15 mg resulted in 27 % and 31 % reduction in serum triglyceride levels respectively compared to 6 % reduction with placebo.

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

In the 4 studies where tirzepatide was not combined with basal insulin (SURPASS-1 to -4), 93.6 % to 100 % of patients who achieved a normal glycaemia of HbA1c < 5.7 % (≤ 39 mmol/mol), at the primary endpoint visit with tirzepatide treatment did so without clinically significant hypoglycaemia. In Study SURPASS-5, 85.9 % of patients treated with tirzepatide who reached HbA1c < 5.7 % (≤ 39 mmol/mol) did so without clinically significant hypoglycaemia.

Special populations

The efficacy of tirzepatide for the treatment of T2DM was not impacted by age, gender, race, ethnicity, region, or by baseline BMI, HbA1c, diabetes duration and level of renal function impairment.

The efficacy of tirzepatide for weight management was not impacted by age, gender, race, ethnicity, region, baseline BMI, and presence or absence of prediabetes.

The efficacy of tirzepatide for the treatment of moderate to severe OSA in patients with obesity was not impacted by age, sex, ethnicity, baseline BMI, or baseline OSA severity.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Mounjaro in one or more subsets of the paediatric population for the treatment of type 2 diabetes mellitus and for weight management (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Tirzepatide consists of 39-amino acids and has a C20 fatty diacid moiety attached, which enables albumin binding and prolongs half-life.

Absorption

Maximum concentration of tirzepatide is reached 8 to 72 hours post dose. Steady state exposure is achieved following 4 weeks of once weekly administration. Tirzepatide exposure increases in a dose proportional manner.

Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm.

Absolute bioavailability of subcutaneous tirzepatide was 80 %.

Distribution

The mean apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with type 2 diabetes is approximately 10.3 L, and 9.7 L in patients with obesity.

Tirzepatide is highly bound to plasma albumin (99 %).

Biotransformation

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

Elimination

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

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

Special populations

Age, gender, race, ethnicity, body weight

Age, gender, race, ethnicity, or body weight do not have a clinically relevant effect on the pharmacokinetics (PK) of tirzepatide. Based on a population PK analysis, the exposure of tirzepatide increases with decreasing body weight; however, the effect of body weight on the PK of tirzepatide does not appear to be clinically relevant.

Renal impairment

Renal impairment does not impact the PK of tirzepatide. The PK of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function and no clinically relevant differences were observed. This was also shown for patients with both type 2 diabetes mellitus and renal impairment based on data from clinical studies.

Hepatic impairment

Hepatic impairment does not impact the PK of tirzepatide. The PK of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function and no clinically relevant differences were observed.

Paediatric population

Tirzepatide has not been studied in paediatric patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeat-dose toxicity or genotoxicity.

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

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 did not produce increased incidences of thyroid C-cell hyperplasia or neoplasia at any dose.

Animal studies with tirzepatide did not indicate direct harmful effects with respect to fertility.

In animal reproduction studies, tirzepatide caused foetal growth reductions and foetal abnormalities at exposures below the MRHD based on AUC. An increased incidence of external, visceral, and skeletal malformations and visceral and skeletal developmental variations were observed in rats. Foetal growth reductions were observed in rats and rabbits. All developmental effects occurred at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pre-filled pen, single-dose; vial, single-dose

Disodium hydrogen phosphate heptahydrate (E339)

Sodium chloride
Concentrated hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

Pre-filled pen (KwikPen), multi-dose

Disodium hydrogen phosphate heptahydrate (E339)
Benzyl alcohol (E1519)
Glycerol
Phenol
Sodium chloride
Concentrated hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Pre-filled pen, single-dose; vial, single-dose

Before use
2 years

Mounjaro may be stored unrefrigerated for up to 21 cumulative days at a temperature below 30 ºC and then the pre-filled pen or vial must be discarded.

Pre-filled pen (KwikPen), multi-dose

Before use
2 years

After first use
30 days. Store unrefrigerated at room temperature below 30 ºC. The pre-filled KwikPen must be discarded 30 days after first use.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC).
Do not freeze.

Pre-filled pen, single-dose; vial, single-dose

Store in original package in order to protect from light.

Pre-filled pen (KwikPen), multi-dose

For storage conditions after first use of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Pre-filled pen, single-dose

Glass syringe encased in a disposable pre-filled pen.

The pre-filled pen has a hidden needle, which will automatically insert into the skin when the injection button is pressed.
Each pre-filled pen contains 0.5 ml of solution.

Pack sizes of 2 pre-filled pens, 4 pre-filled pens and multipack containing 12 (3 packs of 4) pre-filled pens. Not all pack sizes may be marketed.

Vial, single-dose

Clear glass vial with a sealed stopper.
Each vial contains 0.5 ml of solution.
Pack sizes of 1 vial, 4 vials, 12 vials, multipack containing 4 (4 packs of 1) vials or multipack containing 12 (12 packs of 1) vials. Not all pack sizes may be marketed.

Pre-filled pen (KwikPen), multi-dose

Clear glass cartridge encased in a multi-dose pre-filled pen.

Each pre-filled KwikPen contains 2.4 ml of solution for injection (4 doses of 0.6 ml). Each pen has excess volume for priming. However, attempting to inject any leftover medicinal product will result in an incomplete dose even though the pen still has medicinal product left in it. Needles are not included.

Pack sizes of 1 and 3 pre-filled KwikPens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use

Inspect Mounjaro visually before use and discard for particulate matter or discolouration.
Mounjaro that has been frozen must not be used.

Pre-filled pen, single-dose
The pre-filled pen is for single-use only.

The instructions for using the pen, included with the package leaflet, must be followed carefully.

Vial, single-dose
The vial is for single-use only.

The instructions in the package leaflet for how to inject Mounjaro from a vial must be followed carefully.

Pre-filled pen (KwikPen), multi-dose
The pre-filled KwikPen is for multiple doses. Each KwikPen contains 4 doses. Dispose of the pen after 4 weekly doses.

The instructions for using the KwikPen, included with the package leaflet, must be followed carefully.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

8. MARKETING AUTHORISATION NUMBER

EU/1/22/1685/001
EU/1/22/1685/002
EU/1/22/1685/003
EU/1/22/1685/004
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EU/1/22/1685/059
EU/1/22/1685/060

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 September 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu