MOUNJARO KWIKPEN
Tirzepatide

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled pen (KwikPen), multi-dose

Mounjaro KwikPen 2.5 mg/dose 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 KwikPen 5 mg/dose 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 KwikPen 7.5 mg/dose 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 KwikPen 10 mg/dose 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 KwikPen 12.5 mg/dose 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 KwikPen 15 mg/dose 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 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.

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).

4.2 Posology and method of administration

Posology

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

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

The maximum dose is 15 mg once weekly.

Self-monitoring of blood glucose is not needed in order to adjust the dose of tirzepatide.
When tirzepatide is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued.

When tirzepatide is added to existing therapy of a 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 (96 hours) after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

Changing 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 (72 hours).

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.

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.

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

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

Inject Mounjaro subcutaneously in the abdomen, thigh or upper arm.
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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

4.4 Special warnings and precautions for use

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. 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 specificity test 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.

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).

Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with MOUNJARO. If hypersensitivity reactions occur, discontinue use of MOUNJARO; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous serious hypersensitivity reaction to tirzepatide or any of the excipients in MOUNJARO.

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.

Acute Kidney Injury Due to Volume Depletion

There have been postmarketing reports of acute kidney injury, in some cases requiring hemodialysis, in patients treated with GLP-1 receptor agonists, or MOUNJARO. The majority of the reported events occurred in patients who experienced gastrointestinal adverse reactions leading to dehydration such as nausea, vomiting, or diarrhea. Monitor renal function in patients reporting adverse reactions to MOUNJARO that could lead to volume depletion, especially during dosage initiation and escalation of MOUNJARO.

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 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 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 9 completed phase 3 studies, 7 702 patients were exposed to tirzepatide alone or in combination with other glucose lowering medicinal products. The most frequently reported adverse reactions in clinical studies were gastrointestinal disorders, including nausea (very common), diarrhoea (very common), constipation (common) and vomiting (common). In general, these reactions were mostly mild or moderate in severity and occurred more often during dose escalation and decreased over time. (see sections 4.2, 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]		
Vascular disorders		Hypotension[2]		
Gastrointestinal disorders	Nausea, diarrhoea	Abdominal pain, vomiting, dyspepsia, constipation, abdominal distention, Eructation, Flatulence, Gastroesophageal reflux disease	Cholelithiasis, Cholecystitis, Acute pancreatitis	
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	

[#]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

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 the pool of placebo-controlled trials in patients with BMI ≥ 27 kg/m^2 with or without T2DM, sometimes severe (e.g., rash and dermatitis);

hypersensitivity reactions were reported in 5.0 % of tirzepatide-treated patients compared to 2.3 % of placebo-treated patients.

Hypoglycaemia in patients with type 2 diabetes mellitus

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

Clinically significant hypoglycaemia occurred in 10 to 14 % (0.14 to 0.16 events/patient year) of patients when tirzepatide was added to 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 0.03 events/patient year (see table 1 and sections 4.2, 4.4 and 5.1).

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. Gastrointestinal events 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 the placebo-controlled phase 3 studies in patients with BMI ≥ 27 kg/m^2 with or without T2DM, gastrointestinal disorders were increased for tirzepatide 5 mg (51.3 %), 10 mg (55.2 %) and 15 mg (55.6 %) compared with placebo (28.5 %). Nausea occurred in 22.1 %, 28.8 % and 27.9 % versus 8.3 % and diarrhoea in 16.9 %, 19.3 % and 21.7 % versus 8.0 % for tirzepatide 5 mg, 10 mg and 15 mg respectively versus placebo. Gastrointestinal adverse reactions were mostly mild (63 %) or moderate (32.6 %) 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 (2.0 %), 10 mg (4.5 %) and 15 mg (4.3 %) groups compared to the placebo group (0.5 %) discontinued permanently due to the gastrointestinal event.

Gallbladder-related events

In the pool of placebo-controlled phase 3 studies in patients with BMI ≥ 27 kg/m2 with or without T2DM, the overall incidence of cholecystitis and cholecystitis acute was 0.5 % and 0 % for tirzepatide- and placebo-treated patients, respectively.

In the pool of placebo-controlled phase 3 studies in patients with BMI ≥ 27 kg/m2 with or without T2DM, acute gallbladder disease was reported by 1.6 % of tirzepatide-treated patients and 1.0 % of placebo-treated patients. These acute gallbladder events were positively associated with weight reduction.

Immunogenicity

5 025 tirzepatide-treated patients in the T2DM phase 3 clinical studies were assessed for anti-drug antibodies (ADAs). Of these, 51.1 % developed treatment-emergent (TE) ADAs during the on-treatment period. In 38.3 % of the assessed patients, TE ADAs were persistent (ADAs present for a period of 16-weeks or greater). 1.9 % and 2.1 % had neutralizing 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 neutralizing antibodies against native GIP and GLP-1, respectively. There was no evidence of an altered pharmacokinetic profile or an impact on efficacy of tirzepatide associated with the development of ADAs.

6 206 tirzepatide-treated patients with BMI ≥ 27 kg/m^2 with or without T2DM were assessed in the phase 3 clinical studies for anti-drug antibodies (ADAs). Of these, 56.1 % developed treatment-emergent (TE) ADAs during the on-treatment period. In 43.1 % of the assessed patients, TE ADAs were persistent (ADAs present for a period of 16 weeks or greater). 2.2 % and 2.4 % had neutralising antibodies against tirzepatide activity on the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, respectively and 0.8 % and 0.3 % had neutralising antibodies against native GIP and 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 the placebo-controlled phase 3 studies in patients with BMI ≥ 27 kg/m^2 with or without T2DM, 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 in baseline heart rate of > 20 bpm for 2 or more consecutive visits was 1.0 %, 2.4 % and 3.3 %, for tirzepatide 5 mg, 10 mg and 15 mg, respectively, compared with 0.7 % for placebo.

Small mean increases in PR interval were observed with tirzepatide and placebo (mean increase of 0.3 to 1.3 msec and of 0.6 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 (3.9 %, 3.1 %, 3.6 % and 3.3 % 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 the placebo-controlled phase 3 studies in patients with BMI ≥ 27 kg/m^2 with or without T2DM, injection site reactions were increased for tirzepatide (7.2 %) compared with placebo (1.8 %).

Overall, in the phase 3 studies, the most common signs and symptoms of injection site reactions were erythema and pruritus. The maximum severity of injection site reactions for patients was mild (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 the placebo-controlled phase 3 studies in patients with BMI ≥ 27 kg/m^2 with or without T2DM, treatment with tirzepatide resulted in mean increases from baseline in pancreatic amylase of 20 % to 24 % and lipase of 29 % to 35 %. Placebo treated patients had an increase from baseline in amylase of 3.8 % and in lipase of 5.3 %.

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:

Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/ADR

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. 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.

Tirzepatide is 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.

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 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.

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. Reduced food intake with tirzepatide contributes to body weight loss. The body weight reduction is mostly due to reduced fat mass.

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 efficacy 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

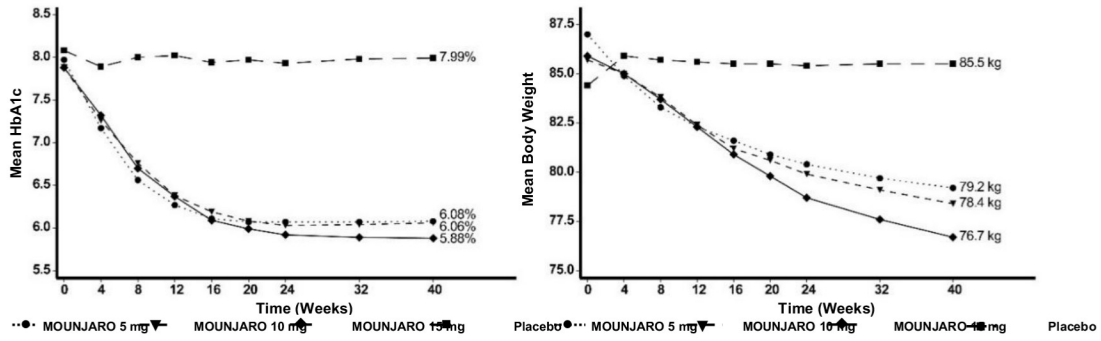

Figure 1. Mean HbA_{1c} (%)and mean body weight (kg) from baseline to week 40

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.

† $p < 0.05$, †† $p < 0.001$ compared to semaglutide 1 mg, not adjusted for multiplicity.

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

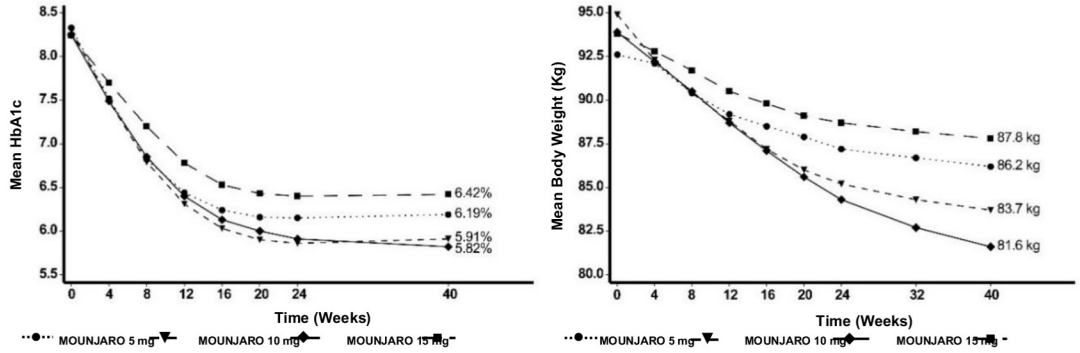

Figure 2. Mean HbA_{1c} (%)and mean body weight (kg) from baseline to week 40.

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.

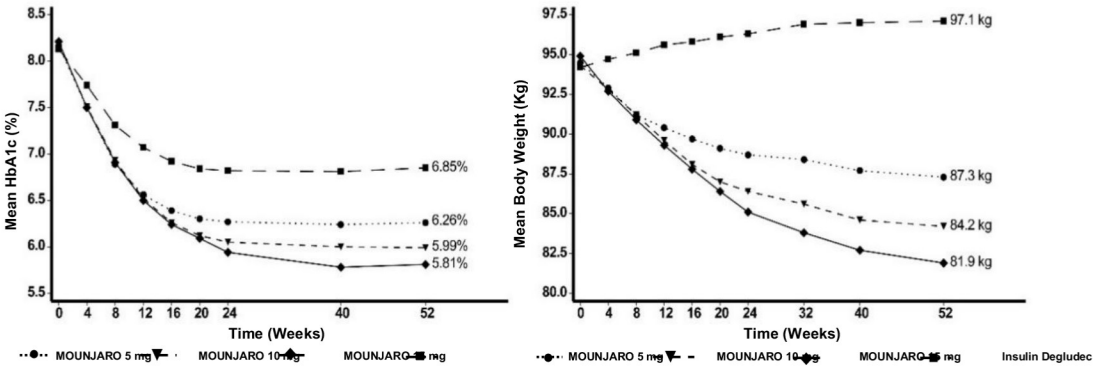

Figure 3. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 52

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.
† $p < 0.05$, †† $p < 0.001$ compared to insulin glargine, not adjusted for multiplicity.
# $p < 0.05$, ## $p < 0.001$ compared to baseline, not adjusted for multiplicity.

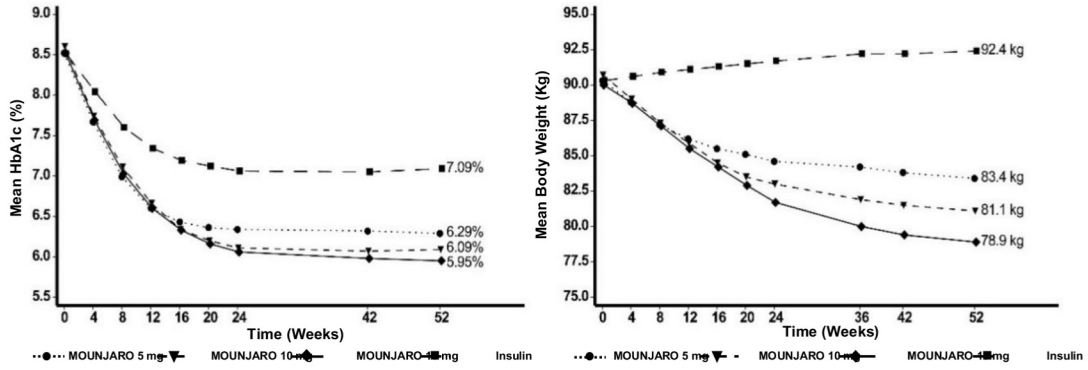

Figure 4. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 52

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.

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

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

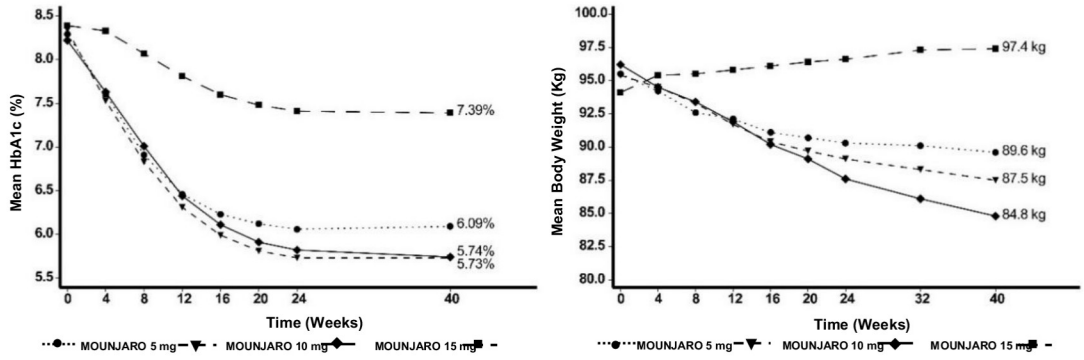

Figure 5. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 40

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, without diabetes mellitus, were evaluated in a randomized double-blinded, placebo-controlled phase 3 study (SURMOUNT-1).

Treatment with tirzepatide demonstrated clinically meaningful and sustained (up to 72 weeks) weight reduction compared with placebo. Furthermore, in SURMOUNT-1, 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 subpopulation of patients with BMI ≥ 27 kg/m^2 in five randomized phase 3 studies (SURPASS-1 to -5). A total of 5 392 patients with BMI ≥ 27 kg/m^2 (3 626 randomized to treatment with tirzepatide) were included in these studies. Subgroup analyses of patients with obesity or overweight in the SURPASS studies (amounting to 86 % of the overall SURPASS-1 to -5 population) showed weight reduction sustained (up to 52 weeks), and a higher percentage of patients achieving weight reduction targets compared to active comparator/placebo.

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, such as treated or untreated dyslipidaemia, hypertension, obstructive sleep apnoea, or cardiovascular disease, were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or placebo. Patients treated with tirzepatide started with 2.5 mg for 4 weeks. The dose of tirzepatide was increased by 2.5 mg every 4 weeks until patients reached their assigned dose. Patients with type 2 diabetes mellitus were excluded. Patients had a mean age of 45 years and 67.5 % were women. At baseline 40.6 % of patients had prediabetes. Mean baseline body weight was 104.8 kg and mean BMI 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.

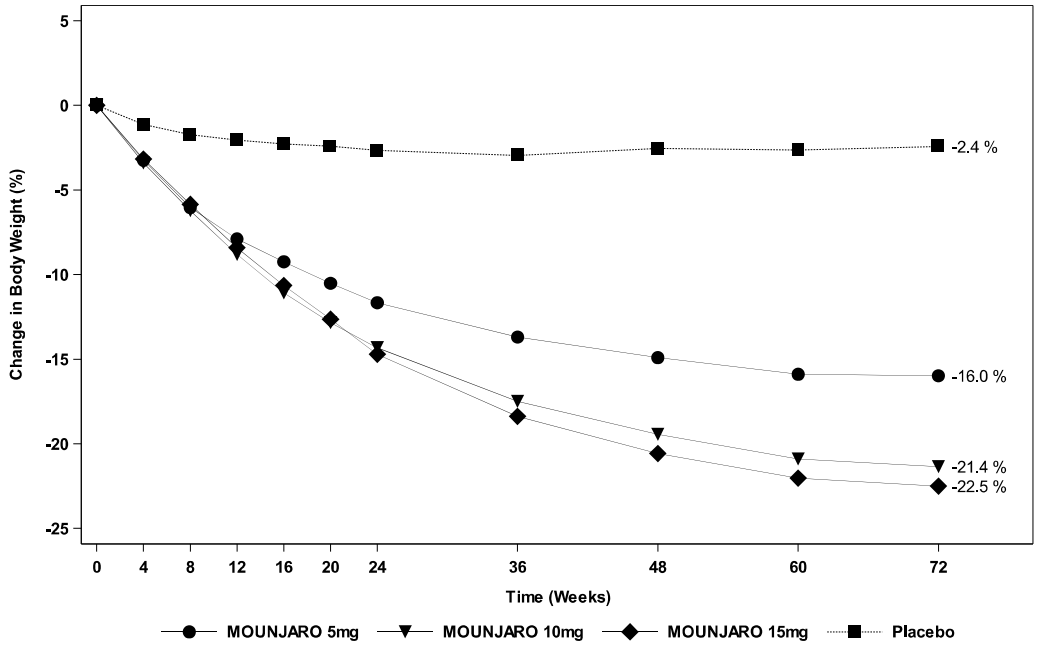

Figure 6. Mean change in body weight (%) from baseline to week 72

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.

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).

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 addition, analysis was conducted for the SURMOUNT-1 study. A total of 14 patients (tirzepatide: 9 [n = 1 896]; placebo:5 [n = 643]) experienced at least one adjudication confirmed MACE: the event rate was similar across placebo and tirzepatide 5 mg and 10 mg groups. There was no event in tirzepatide 15 mg group.

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 the 72 week placebo-controlled phase 3 study in patients with obesity or overweight without T2DM, treatment with tirzepatide resulted in a mean decrease in systolic and diastolic blood pressure of 7 to 8 mmHg and 5 to 6 mmHg, respectively. There was a mean decrease in systolic and diastolic blood pressure of 1 mmHg each in placebo treated patients.

Heart Rate
In the placebo controlled phase 3 studies, treatment with tirzepatide resulted in a mean increase in heart rate of 2 to 4 beats per minute. There was a mean increase in heart rate of 1 beat per minute in placebo-treated patients.

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 hours 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, 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.

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.

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

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 (KwikPen), multi-dose

Dibasic sodium phosphate heptahydrate
Benzyl alcohol
Glycerol
Phenol
Sodium chloride
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 (KwikPen), multi-dose

Before use
2 years

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

6.4 Special precautions for storage

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

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 (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 pre-filled KwikPen.

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 (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. PRESENTATION

Mounjaro KwikPen 2.5 mg/dose, box of 1 multi-dose pre-filled pen @ 2.4 mL, Reg. No.: DKIxxxxxxxxxx

Mounjaro KwikPen 5 mg/dose, box of 1 multi-dose pre-filled pen @ 2.4 mL, Reg. No.: DKIxxxxxxxxxx
Mounjaro KwikPen 7.5 mg/dose, box of 1 multi-dose pre-filled pen @ 2.4 mL, Reg. No.: DKIxxxxxxxxxx
Mounjaro KwikPen 10 mg/dose, box of 1 multi-dose pre-filled pen @ 2.4 mL, Reg. No.: DKIxxxxxxxxxx
Mounjaro KwikPen 12.5 mg/dose, box of 1 multi-dose pre-filled pen @ 2.4 mL, Reg. No.: DKIxxxxxxxxxx
Mounjaro KwikPen 15 mg/dose, box of 1 multi-dose pre-filled pen @ 2.4 mL, Reg. No.: DKIxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

Manufactured by:
Eli Lilly Italia SpA
Via Antonio Gramsci 731/733
Sesto Fiorentino FI 50019
Italy

Released by:
Lilly, S.A.
Avda de la Industria, 30
Alcobendas
28108 Madrid
Spain

Registered by:
PT Wigo Health Indonesia
Kabupaten Semarang
Indonesia

MOUNJARO KWIKPEN

Mounjaro KwikPen 2,5 mg/dosis larutan injeksi dalam *pre-filled pen*
Mounjaro KwikPen 5 mg/dosis larutan injeksi dalam *pre-filled pen*
Mounjaro KwikPen 7,5 mg/dosis larutan injeksi dalam *pre-filled pen*
Mounjaro KwikPen 10 mg/dosis larutan injeksi dalam *pre-filled pen*
Mounjaro KwikPen 12,5 mg/dosis larutan injeksi dalam *pre-filled pen*
Mounjaro KwikPen 15 mg/dosis larutan injeksi dalam *pre-filled pen*
Tirzepatide

Informasi Produk untuk Pasien

Bacalah seluruh *leaflet* ini dengan saksama sebelum Anda menggunakan obat ini karena *leaflet* ini berisi informasi yang penting untuk Anda.
- Simpanlah *leaflet* ini. Anda mungkin perlu untuk membacanya kembali.
- Jika Anda mempunyai pertanyaan lebih lanjut, silakan bertanya kepada dokter, apoteker atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan kepada orang lain. Ini mungkin dapat membahayakan mereka, walaupun gejala-gejala penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping, beritahu dokter, apoteker atau perawat Anda. Hal ini termasuk efek samping lain yang mungkin terjadi yang belum tercantum di *leaflet* ini. Silakan lihat bagian 4.

Apa isi *leaflet* ini

1. Apa itu Mounjaro KwikPen dan apa kegunaannya

Mounjaro adalah larutan bening, tidak berwarna hingga agak kuning, untuk injeksi dalam *pre-filled pen KwikPen*. Mounjaro adalah suatu obat yang mengandung zat aktif yang disebut tirzepatide dan digunakan untuk mengobati diabetes melitus tipe 2 pada orang dewasa.

Diabetes tipe 2 adalah suatu kondisi di mana tubuh Anda tidak memproduksi cukup insulin, dan insulin yang diproduksi tubuh Anda tidak bekerja sebagaimana mestinya.

Ketika hal ini terjadi, gula (glukosa) menumpuk di dalam darah. Pengobatan diabetes yang efektif, dengan kontrol gula darah yang baik, mencegah komplikasi jangka panjang dari penyakit diabetes Anda.

Mounjaro juga digunakan untuk mengobati orang dewasa dengan obesitas atau kelebihan berat badan (dengan BMI minimal 27 kg/m^2). Mounjaro memengaruhi pengaturan nafsu makan, yang dapat membantu Anda mengurangi porsi makan dan menurunkan berat badan.

Pada diabetes tipe 2, Mounjaro digunakan:
- secara tunggal jika gula darah Anda tidak dikontrol dengan baik hanya dengan diet dan olahraga, dan Anda tidak dapat mengonsumsi metformin (obat diabetes lainnya).
- atau dengan obat lain untuk diabetes ketika obat tersebut tidak cukup untuk mengontrol kadar gula darah Anda. Obat-obatan lain tersebut dapat berupa obat yang diminum dan/atau insulin yang diberikan melalui suntikan.

Mounjaro juga digunakan bersama diet dan olahraga untuk menurunkan berat badan dan membantu menjaga berat badan tetap terkendali pada orang dewasa yang memiliki:
- BMI 30 kg/m² atau lebih (obesitas) atau
- BMI minimal 27 kg/m² tetapi kurang dari 30 kg/m² (kelebihan berat badan) dan masalah kesehatan terkait berat badan (seperti pradiabetes, diabetes tipe 2, tekanan darah tinggi, kadar lemak abnormal dalam darah, masalah pernapasan saat tidur yang disebut "*Obstructive Sleep Apnea"* atau riwayat serangan jantung, stroke atau masalah pembuluh darah).

BMI (Indeks Massa Tubuh) adalah ukuran berat badan Anda dalam kaitannya dengan tinggi badan Anda.

Penting untuk terus mengikuti saran tentang diet dan olahraga yang diberikan oleh dokter, apoteker atau perawat Anda.

2. Apa yang perlu Anda ketahui sebelum menggunakan Mounjaro KwikPen

Jangan menggunakan Mounjaro KwikPen
- jika Anda alergi terhadap tirzepatide atau bahan lain dari obat ini (tercantum dalam bagian 6).
- Anda atau siapa pun dalam keluarga Anda pernah menderita kanker tiroid yang disebut *medullary thyroid carcinoma (MTC)* atau jika Anda menderita kondisi sistem endokrin yang disebut *Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)*.

Peringatan dan perhatian
Bicaralah dengan dokter, perawat atau apoteker Anda sebelum menggunakan Mounjaro jika:

- Anda memiliki masalah berat dengan pencernaan makanan atau makanan berada di dalam perut Anda lebih lama dari biasanya (termasuk gastroparesis berat).
- Anda pernah mengalami pankreatitis (peradangan pankreas) yang menyebabkan nyeri hebat di perut dan punggung yang tidak kunjung sembuh.
- jika Anda memiliki masalah dengan mata Anda (retinopati diabetik atau edema makula).
- Anda menggunakan sulfonilurea atau insulin untuk diabetes Anda, karena dapat terjadi gula darah rendah (hipoglikemia). Dokter Anda mungkin perlu mengubah dosis obat-obat tersebut untuk mengurangi risiko ini.

Saat memulai pengobatan dengan Mounjaro, dalam beberapa kasus Anda mungkin mengalami kehilangan cairan/dehidrasi, misalnya dalam kasus muntah, mual dan/atau diare yang dapat menyebabkan penurunan fungsi ginjal. Penting untuk menghindari dehidrasi dengan minum banyak cairan. Hubungi dokter Anda jika Anda memiliki pertanyaan atau kekhawatiran.

Jika Anda tahu bahwa Anda akan menjalani operasi yang mengharuskan Anda dibius (tidur), harap beritahu dokter Anda bahwa Anda sedang menggunakan Mounjaro.

Kemungkinan tumor tiroid, termasuk kanker. Beri tahu penyedia layanan kesehatan Anda jika Anda mengalami benjolan atau pembengkakan di leher, suara serak, kesulitan menelan, atau sesak napas. Ini mungkin merupakan gejala kanker tiroid. Dalam penelitian pada tikus, MOUNJARO dan obat-obatan

yang bekerja seperti MOUNJARO menyebabkan tumor tiroid, termasuk kanker tiroid. Belum diketahui apakah MOUNJARO akan menyebabkan tumor tiroid, atau jenis kanker tiroid yang disebut karsinoma tiroid meduler (MTC) pada manusia.

Reaksi alergi serius. Hentikan penggunaan MOUNJARO dan segera dapatkan bantuan medis jika Anda mengalami gejala reaksi alergi serius, termasuk:
- pembengkakan pada wajah, bibir, lidah atau tenggorokan
- kesulitan bernapas atau menelan
- ruam atau gatal parah
- pingsan atau merasa pusing
- detak jantung sangat cepat

Dehidrasi yang menyebabkan masalah ginjal. Diare, mual dan muntah dapat menyebabkan kehilangan cairan (dehidrasi) yang dapat menyebabkan masalah ginjal. Penting bagi Anda untuk minum cairan untuk membantu mengurangi risiko dehidrasi.

Anak-anak dan remaja
Obat ini tidak untuk digunakan pada anak dan remaja berusia dibawah 18 tahun karena belum ada studi penggunaan pada rentang usia tersebut.

Obat-obat lainnya dan Mounjaro
Beritahukan dokter, apoteker atau perawat Anda jika Anda sedang menggunakan, baru saja menggunakan atau mungkin menggunakan obat-obat lain.

Kehamilan
Jika Anda sedang hamil, berpikir Anda mungkin hamil atau berencana untuk memiliki anak, mintalah saran dokter Anda sebelum menggunakan obat ini. ini. Obat ini sebaiknya tidak digunakan selama masa kehamilan dikarenakan efek obat ini terhadap janin tidak diketahui. Sehingga, disarankan untuk menggunkan kontrasepsi selama menggunakan obat ini.

Menyusui
Tidak diketahui apakah tirzepatide masuk kedalam air susu ibu. Risiko pada bayi baru lahir/bayi tidak dapat dikesampingkan. Jika Anda sedang menyusui atau berencana untuk menyusui, bicaralah dengan dokter sebelum menggunakan obat ini. Anda dan dokter Anda sebaiknya menentukan apakah Anda akan berhenti menyusui atau menunda penggunaan Mounjaro.

Mengemudi dan mengoperasikan mesin
Obat ini tidak berpengaruh terhadap kemampuan Anda dalam mengemudi dan mengoperasikan mesin. Namun, jika Anda menggunakan Mounjaro dalam kombinasi dengan sulfonilurea atau insulin, gula darah rendah (hipoglikemia) dapat terjadi yang mana dapat mengurangi kemampuan Anda untuk berkonsentrasi. Hindari mengemudi atau mengoperasikan mesin jika Anda mengalami tanda-tanda gula darah rendah seperti sakit sakit kepala, mengantuk, lemas, pusing, merasa lapar, bingung, mudah tersinggung, detak jantung cepat dan berkeringat (lihat bagian 4). Lihat bagian 2, 'Peringatan dan perhatian' untuk informasi tentang peningkatan risiko gula darah rendah. Bicaralah dengan dokter Anda untuk informasi lebih lanjut.

Mounjaro KwikPen mengandung sodium (natrium)
Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per dosis, pada dasarnya bisa dikatakan “bebas natrium”.

Mounjaro KwikPen mengandung *benzyl alcohol*

Obat ini mengandung 5,4 mg *benzyl alcohol* dalam setiap 0,6 ml dosis. *Benzyl alcohol* dapat menyebabkan reaksi alergi.

Mintalah saran dari dokter, perawat, atau apoteker jika Anda sedang hamil atau menyusui atau jika Anda memiliki penyakit hati atau ginjal. Hal ini karena sejumlah besar *benzyl alcohol* dapat menumpuk di dalam tubuh Anda dan dapat menyebabkan efek samping (disebut "asidosis metabolik").

3. Bagaimana cara menggunakan Mounjaro KwikPen

Selalu gunakan obat ini tepat seperti yang dokter atau apeteker Anda katakan kepada Anda. Konsultasikan dengan dokter, atau apoteker Anda jika Anda tidak yakin bagaimana cara menggunakan obat ini.

Berapa banyak yang digunakan
Dosis awal adalah 2,5 mg seminggu sekali selama empat minggu. Setelah empat minggu, dokter Anda akan meningkatkan dosis Anda menjadi 5 mg seminggu sekali.

Dokter Anda dapat meningkatkan dosis Anda dengan peningkatan 2,5 mg menjadi 7,5 mg, 10 mg, 12,5 mg atau 15 mg seminggu sekali jika Anda membutuhkannya. Dalam setiap kasus Anda harus tetap pada dosis tertentu selama minimal 4 minggu sebelum melanjutkan ke dosis yang lebih tinggi.

Jangan mengubah dosis Anda kecuali atas saran dokter Anda.

Memilih waktu menggunakan Mounjaro

Anda dapat menggunakan pen Anda kapan saja sepanjang hari, dengan atau tanpa makanan. Anda harus menggunakannya pada hari yang sama setiap minggunya jika memungkinkan. Untuk membantu Anda mengingat kapan harus menggunakan Mounjaro, Anda bisa menandainya di kalender.

Jika perlu, Anda dapat mengubah hari suntikan Mounjaro mingguan Anda, asalkan sudah lewat setidaknya 3 hari sejak suntikan terakhir Anda. Setelah memilih hari pemberian dosis baru, lanjutkan dengan pemberian dosis seminggu sekali pada hari baru tersebut.

Bagaimana cara menyuntikkan Mounjaro KwikPen

Mounjaro disuntikkan di bawah kulit (suntikan subkutan) pada daerah perut minimal 5 cm dari pusar atau paha bagian atas atau lengan bagian atas. Anda mungkin memerlukan bantuan orang lain jika Anda ingin menyuntikkan di lengan bagian atas.

Jika Anda ingin melakukannya, Anda dapat menggunakan area tubuh yang sama setiap minggu. Tetapi pastikan untuk memilih tempat suntikan yang berbeda dalam area itu. Jika Anda juga menyuntikkan insulin, pilih tempat suntikan yang berbeda untuk suntikan tersebut.

Baca "Petunjuk Penggunaan" untuk pen dengan cermat sebelum menggunakan Mounjaro KwikPen.

Mengecek kadar glukosa darah
Jika Anda menggunakan Mounjaro dengan sulfonilurea atau insulin, penting bagi Anda untuk mengecek kadar glukosa darah sesuai petunjuk dokter, perawat, atau apoteker Anda (lihat bagian 2, ‘Peringatan dan tindakan pencegahan’).

Jika Anda menggunakan Mounjaro melebihi yang seharusnya

Segera beritahu dokter Anda jika Anda menggunakan Mounjaro lebih dari yang seharusnya. Terlalu banyak menggunakan obat ini dapat membuat gula darah Anda terlalu rendah (hipoglikemia) dan dapat membuat Anda merasa sakit atau menjadi sakit.

Jika Anda lupa menggunakan Mounjaro
Jika Anda lupa menyuntikkan dosis dan,
- sudah **4 hari atau kurang** sejak Anda seharusnya menggunakan Mounjaro, gunakan segera setelah Anda ingat. Kemudian suntikkan dosis berikutnya seperti biasa pada hari yang dijadwalkan.
- Jika sudah **lebih dari 4 hari** sejak Anda seharusnya menggunakan Mounjaro, lewati dosis yang terlupa. Kemudian suntikkan dosis berikutnya seperti biasa pada hari yang dijadwalkan.

Jangan gunakan dosis ganda untuk mengganti dosis yang terlupakan. Waktu minimal antara dua dosis harus setidaknya 3 hari.

Jika Anda berhenti menggunakan Mounjaro
Anda tidak disarankan untuk berhenti menggunakan Mounjaro tanpa berbicara dengan dokter Anda terlebih dahulu. Jika Anda menghentikan penggunaan Mounjaro dan Anda mempunyai diabetes tipe 2, kadar gula darah Anda dapat meningkat.

Jika Anda mempunyai pertanyaan lebih lanjut terkait penggunaan obat ini, tanyakan ke dokter, apoteker atau perawat Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Efek samping yang serius

Tidak umum terjadi (dapat memengaruhi hingga 1 dari 100 orang)
- Radang pada pankreas (pankreatitis akut) yang dapat menyebabkan nyeri hebat di perut dan punggung yang tidak kunjung hilang. Anda harus segera menemui dokter jika mengalami gejala tersebut.

Jarang terjadi (dapat memengaruhi hingga 1 dari 1.000 orang)
- Reaksi alergi berat (misalnya reaksi anafilaksis, angioedema). Anda harus segera mendapatkan pertolongan medis dan memberi tahu dokter jika mengalami gejala seperti masalah pernapasan, pembengkakan cepat pada bibir, lidah, dan/atau tenggorokan disertai kesulitan menelan dan detak jantung cepat.

Efek samping lainnya

Sangat umum terjadi (dapat memengaruhi lebih dari 1 diantara 10 orang):
- mual
- diare

Efek samping ini biasanya tidak parah. Paling umum terjadi ketika pertama kali memulai tirzepatide tetapi menurun seiring waktu pada kebanyakan pasien.

- Gula darah rendah (hipoglikemia) sangat umum ketika tirzepatide digunakan dengan obat-obatan yang mengandung sulfonilurea dan/atau insulin. Jika Anda menggunakan sulfonilurea atau insulin untuk diabetes tipe 2, dosisnya mungkin perlu diturunkan saat Anda menggunakan tirzepatide.
- Gejala gula darah rendah mungkin termasuk sakit kepala, mengantuk, lemah, pusing, merasa lapar, kebingungan, mudah marah, detak jantung cepat dan berkeringat. Dokter Anda harus memberi tahu Anda cara mengobati gula darah rendah.

Umum terjadi (dapat memengaruhi hingga 1 diantara 10 orang):
- Gula darah rendah (hipoglikemia) ketika tirzepatide digunakan untuk diabetes tipe 2 dengan metformin dan *sodium-glucose co transporter 2 inhibitor*
- Reaksi alergi (hipersensitivitas) (misalnya, ruam, gatal dan eksim)
- Pusing dilaporkan pada pasien yang menjalani perawatan manajemen berat badan
- Tekanan darah rendah dilaporkan pada pasien yang menjalani perawatan manajemen berat badan
- Merasa kurang lapar (nafsu makan berkurang) dilaporkan pada pasien yang menjalani perawatan diabetes tipe 2
- Nyeri perut
- Muntah - ini biasanya hilang seiring waktu
- Gangguan pencernaan (dispepsia)
- Sembelit
- Perut kembung
- Bersendawa (eruktasi),
- Perut bergas
- Refluks atau rasa panas di dalam perut (juga disebut penyakit *gastroesophageal reflux* - GERD) - penyakit yang disebabkan oleh asam lambung yang naik ke saluran dari perut ke mulut Anda
- Kerontokan dilaporkan pada pasien yang menjalani perawatan manajemen berat badan
- Merasa lelah
- Reaksi di tempat suntikan (misalnya ruam atau kemerahan)
- Denyut nadi cepat
- Peningkatan kadar enzim pankreas (seperti lipase dan amilase) dalam darah

Tidak umum terjadi (dapat memengaruhi hingga 1 diantara 100 orang):
- Gula darah rendah (hipoglikemia) ketika tirzepatide digunakan dengan metformin untuk diabetes tipe 2.
- Batu empedu
- Peradangan pada kantong empedu
- Penurunan berat badan dilaporkan pada pasien yang menjalani perawatan diabetes tipe 2
- Nyeri di tempat suntikan
- Peningkatan kadar kalsitonin dalam darah

Pelaporan efek samping
Jika Anda mengalami efek samping, beritahukan dokter, apoteker atau perawat Anda. Hal ini termasuk kemungkinan efek samping yang belum tercantum di *leaflet* ini. Anda juga dapat melaporkan keluhan efek samping secara langsung ke Industri Farmasi melalui kontak berikut: Telepon: +62 21 21684084 atau Email: IDsafety@zuelligpharma.com. Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi lebih mengenai keamanan dari obat ini.

5. Bagaimana cara menyimpan Mounjaro KwikPen

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kadaluarsa yang tercantum di label pen dan bagian luar dus setelah tulisan EXP. Tanggal kadaluarsa merujuk pada hari terakhir di bulan tersebut.

Simpan dalam lemari pendingin (2°C – 8°C). Jangan dibekukan. Jika pen sudah membeku, JANGAN DIGUNAKAN.

Simpan dalam kemasan aslinya agar terlindung dari cahaya.

Mounjaro KwikPen dapat disimpan diluar lemari pendingin pada suhu dibawah 30°C sampai 30 hari setelah penggunaan pertama dan setelahnya harus dibuang.

Jangan gunakan obat ini jika pen rusak, atau obatnya keruh, berubah warna atau terdapat partikel di dalamnya.

Jangan buang obat ini melalui saluran pembuangan air atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana cara membuang obat-obatan yang sudah tidak digunakan. Tindakan ini dapat membantu untuk melindungi lingkungan.

6. Isi dari kemasan dan informasi lainnya

Apa isi Mounjaro KwikPen
Bahan aktifnya adalah tirzepatide.

- *Mounjaro KwikPen 2,5 mg/dosis:* Setiap dosis mengandung 2,5 mg tirzepatide dalam 0,6 mL larutan. Setiap *multi-dose pre-filled pen* mengandung 10 mg tirzepatide dalam 2,4 mL (4,17 mg/mL). Setiap pen menghasilkan 4 dosis masing-masing 2,5 mg.
- *Mounjaro KwikPen 5 mg/dosis:* Setiap dosis mengandung 5 mg tirzepatide dalam 0,6 mL larutan. Setiap *multi-dose pre-filled pen* mengandung 20 mg tirzepatide dalam 2,4 mL (8,33 mg/mL). Setiap pen menghasilkan 4 dosis masing-masing 5 mg.
- *Mounjaro KwikPen 7,5 mg/dosis:* Setiap dosis mengandung 7,5 mg tirzepatide dalam 0,6 mL larutan. Setiap *multi-dose pre-filled pen* mengandung 30 mg tirzepatide dalam 2,4 mL (12,5 mg/mL). Setiap pen menghasilkan 4 dosis masing-masing 7,5 mg.
- *Mounjaro KwikPen 10 mg/dosis:* Setiap dosis mengandung 10 mg tirzepatide dalam 0,6 mL larutan. Setiap *multi-dose pre-filled pen* mengandung 40 mg tirzepatide dalam 2,4 mL (16,7 mg/mL). Setiap pen menghasilkan 4 dosis masing-masing 10 mg.
- *Mounjaro KwikPen 12,5 mg/dosis:* Setiap dosis mengandung 12,5 mg tirzepatide dalam 0,6 mL larutan. Setiap *multi-dose pre-filled pen* mengandung 50 mg tirzepatide dalam 2,4 mL (20,8 mg/mL). Setiap pen menghasilkan 4 dosis masing-masing 12,5 mg.
- *Mounjaro KwikPen 15 mg/dosis:* Setiap dosis mengandung 15 mg tirzepatide dalam 0,6 mL larutan. Setiap *multi-dose pre-filled pen* mengandung 60 mg tirzepatide dalam 2,4 mL (25 mg/mL). Setiap pen menghasilkan 4 dosis masing-masing 15 mg.

Bahan lainnya adalah *dibasic sodium phosphate heptahydrate, benzyl alcohol* (lihat bagian 2 ‘Mounjaro mengandung *benzyl alcohol’* untuk informasi lebih lanjut)*, glycerol, phenol, sodium chloride, sodium hydroxide* (lihat bagian 2 ‘Mounjaro mengandung natrium’ untuk informasi lebih lanjut)*; hydrochloric acid and water for injections.*

Seperti apa rupa Mounjaro dan isi kemasannya
Setiap KwikPen berisi 2,4 mL larutan untuk injeksi (4 dosis masing-masing 0,6 mL), dan kelebihan untuk *priming*.

Tidak termasuk jarum suntik.
Kemasan berisi 1 KwikPen.

Mounjaro KwikPen 2,5 mg/dosis, dus @ 1 *multi-dose pre-filled pen* @ 2,4 mL, Reg. No.: DKIxxxxxxxxxx
Mounjaro KwikPen 5 mg/dosis, dus @1 *multi-dose pre-filled pen* @ 2,4 mL, Reg. No.: DKIxxxxxxxxxx
Mounjaro KwikPen 7,5 mg/dosis, dus @ 1 *multi-dose pre-filled pen* @ 2,4 mL, Reg. No.: DKIxxxxxxxxxx
Mounjaro KwikPen 10 mg/dosis, dus @ 1 *multi-dose pre-filled pen* @ 2,4 mL, Reg. No.: DKIxxxxxxxxxx
Mounjaro KwikPen 12,5 mg/dosis, dus @ 1 *multi-dose pre-filled pen* @ 2,4 mL, Reg. No.: DKIxxxxxxxxxx
Mounjaro KwikPen 15 mg/dosis, dus @ 1 *multi-dose pre-filled pen* @ 2,4 mL, Reg. No.: DKIxxxxxxxxxx

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