swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Mounjaro

International non-proprietary name: tirzepatide

Pharmaceutical form: solution for injection in a prefilled pen

Dosage strength(s): 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg

Route(s) of administration: subcutaneous

Marketing authorisation holder: Eli Lilly (Suisse) SA

Marketing authorisation no.: 68726

Decision and decision date: extension of therapeutic indication approved on 9 July 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BMI	Body mass index
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CV	Cardiovascular
CYP	Cytochrome P450
DDI	Drug-drug interaction
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
E_{max}	Maximum effect
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FFM	Fat-free mass
GI	Gastrointestinal
GLP	Good Laboratory Practice
GLP1RA	Glucagon-like peptide 1 receptor agonists
HbA1c	Glycosylated haemoglobin A1c
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
I_{max}	Maximum inhibitory response
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NAB	Neutralising antibody
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
T_{max}	Time to peak drug concentration

TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TZP	Tirzepatide

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic 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) and in the presence of at least 1 weight-related comorbidity condition (e.g. hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus.)

2.2.2 Approved indication

Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management, including weight loss and weight maintenance, in adults with an initial body mass index (BMI) of
- ≥30 kg/m2 (obesity) or
- ≥27 kg/m2 to < 30kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition (e.g. hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	7 July 2023
Formal objection	3 August 2023
Response to formal objection	14 August 2023
Formal control completed	7 September 2023
List of Questions (LoQ)	10 January 2024
Response to LoQ	12 February 2024
Preliminary decision	24 April 2024
Response to preliminary decision	23 May 2024
Final decision	9 July 2024
Decision	approval

3 Medical context

Globally, obesity and overweight are largely on the rise. These conditions not only impact physical abilities, but can also cause various secondary disorders including type 2 diabetes mellitus (T2DM), cardiovascular (CV) disease, and cancer.

4 Nonclinical aspects

To support the requested extension of the indication, the applicant assessed in a new *in vivo* nonclinical study the toxicity and qualified levels of the impurities (D-Ser32/C-terminal, Gln19, and Gln24 deamidation impurities) that were newly identified due to changes in the impurity identification methods.
The effects observed were consistent with the pharmacology of tirzepatide and the findings in repeat-dose toxicology studies conducted with tirzepatide. No novel or exacerbated toxicities were observed.

There are no changes with regard to posology and method of administration.

This application is based on results of efficacy data from an international pivotal Phase 3 study (SURMOUNT-1) and five supporting Phase 3 studies (SURPASS-1 to 5) in participants with T2DM with a BMI ≥ 27 kg/m^2. Efficacy for the proposed indication is to be clinically assessed.

Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.

From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

The impact of tirzepatide on gastric emptying in overweight/obese non-diabetic and overweight/obese T2DM subjects was investigated using paracetamol absorption as a pharmacodynamic endpoint. Tirzepatide doses were 5 mg (days 1 and 8), 10 mg (days 15, 22, and 29), and 15 mg (day 36). The majority of the non-diabetic subjects (61.1%) was overweight, while the majority of the T2DM subjects (66.7%) was obese.

Paracetamol C_{max} was reduced by 55.4% after administration of 5 mg tirzepatide in the overall subject population. The effect was attenuated over time to a reduction of 32.1% after 15 mg tirzepatide. The reductions in C_{max} were accompanied by delays in T_{max} (1 h after 5 mg tirzepatide, 0.5 h after 15 mg). The effect of tirzepatide on paracetamol AUC was small.

These results are in agreement with the data from the T2DM patient population included in the information for health care professionals.

The effect of tirzepatide on paracetamol AUC was comparable for overweight/obese T2DM and overweight/obese non-T2DM subjects. The effect on paracetamol C_{max} plus 5 mg tirzepatide was comparable as well, but in combination with 15 mg tirzepatide, it was more pronounced in T2DM subjects. The delay in T_{max} was the same for both groups after 15 mg tirzepatide, but after 5 mg, it was more pronounced in overweight/obese non-T2DM subjects.

Special populations

The pharmacokinetics of tirzepatide in overweight or obese patients was investigated in a popPK analysis.

The PK dataset included 1880 patients with a mean age of 45 years (range 18 – 84 years) and a mean body weight of 105 kg (range 60.1 – 214 kg). The majority of the patients was female (67.7%) and Caucasian (70.7%).

The majority (93.8%) of the patients was younger than 65 years old, 5.6% of the patients were at least 65 years old and less than 75 years old, and 5 (0.27%) participants were at least 75 years old. The majority (66%) of the patients had a baseline eGFR greater than 90 mL/min/1.73m². There were 32% patients with a baseline eGFR of at least 60 and less than 90 mL/min/1.73m², and 2% patients with a baseline eGFR of at least 30 and less than 60 mL/min/1.73m².

The starting point of model development was the popPK model developed for T2DM.

Covariates evaluated for their possible impact on tirzepatide PK were injection site, age, albumin, AST, ALT, body size, eGFR, race, sex, and ADA.

The final model was a 2-compartment model with first-order absorption and elimination. The only covariate reaching statistical significance was body weight on clearance and volume terms. The model estimated the fraction of fat mass as well. The model described the data reasonably well.

ADA status, ADA titre, or NAB status had no meaningful effect on tirzepatide PK.

Tirzepatide half-life was 5.7 days, with tirzepatide concentrations reaching the limit of quantitation (2 ng/mL) by 4 weeks after a steady-state dose. The accumulation ratio after multiple dosing was approximately 1.7. There were no major differences in tirzepatide exposures between overweight/obese and T2DM patients.

Simulations with the final model indicated an approximately 1.1% change in tirzepatide exposures per kg body weight.

Pharmacodynamics

MECHANISM OF ACTION AND PRIMARY PHARMACOLOGY

Tirzepatide reduced mean plasma glucose levels in both non-diabetic and T2DM subjects. The effect decreased over time. It was more pronounced in T2DM subjects than in non-diabetic subjects

Tirzepatide also decreased mean HbA1c levels. Again, this effect was more pronounced in T2DM subjects compared to non-diabetic subjects.

The weight loss and decrease in BMI due to tirzepatide was larger in non-diabetic than in T2DM subjects, while the reduction of the waist circumference was larger in T2DM subjects.

EXPOSURE EFFICACY/SAFETY RELATIONSHIP

Efficacy

The relationship between tirzepatide plasma concentrations and body weight in overweight or obese patients without T2DM was investigated in a popPKPD analysis.

The PKPD dataset included 2539 patients with a mean age of 44.9 years (range 18 – 84 years) and a mean body weight of 105 kg (range 60.1 – 214 kg). The majority of the patients was female (67.7%) and Caucasian (70.6%).

As in the popPK model, the structural PKPD body weight model was adopted from the T2DM indication. It was an indirect effect model with fat mass and fat-free mass (FFM) as dependent variables.

The covariates evaluated were age, ethnicity, race, sex, nausea/vomiting/diarrhoea incidence, titre of anti-tirzepatide antibody, baseline HbA1c, and baseline waist circumference.

The final model included a time-varying placebo effect. The drug effect was described by an E_{max} model. Covariates included in the final model were gender and Asian origin.

The final model described the data reasonably well.

Tirzepatide caused dose/concentration-dependent weight loss, predominantly due to a reduction in fat mass (about 3 times more than FFM). The typical ‘half-life’ for weight reduction was estimated to be about 22 weeks, i.e. it would take about 2 years on a stable dose for body weight to get to a new steady state. The placebo effect waned over time, with a half-life of about 40 weeks.

The mean predicted weight reduction after 72 weeks of treatment expressed as a % change from baseline ranged from -4.62% after placebo to -22.5% after 15 mg tirzepatide. The mean predicted decrease in FFM from baseline after 15 mg tirzepatide was -13.9%, while the fat mass was reduced by -33.3%.

The absolute change from baseline in body weight was larger for patients with a higher baseline body weight, but the percentage change from baseline was larger for patients with a lower baseline body weight.

Females had a 31% lower baseline FFM than males. Females also had a 5% higher baseline fat mass than males. Females had a higher I_{max} and IC50 relative to males. The net effect of this was a higher weight loss in females compared to males.

Asian patients were estimated to have 11% lower and 25% lower FFM and fat mass at baseline, respectively.

The overall weight loss was smaller in T2DM patients compared to overweight/obese patients without T2DM, but in both populations, the weight loss was due to loss of fat mass rather than FFM.

Safety

The relationship between tirzepatide plasma concentrations and the prevalence of nausea, vomiting, and diarrhoea in overweight or obese patients was investigated in a popPKPD analysis.

The PKPD dataset was the same as for efficacy.

As in the popPK and the body weight PKPD models, the structural PKPD AE models were adopted from the T2DM indication. They were discrete-time Markow models estimating the transition probabilities between AE states and the impact of drug effects and covariates on these probabilities. Tolerance components were included to describe tachyphylaxis that develops with sustained drug exposure.

The final model for nausea and vomiting included sex and race as covariates. Women develop tolerance slower than men, resulting in a higher and more persistent probability of nausea and vomiting, and Caucasian patients had an increase in baseline probability of mild nausea relative to non-Caucasians. The final model for diarrhoea did not include any covariates.

5.2 Efficacy

Reduction in body weight served as a secondary efficacy endpoint across prior Phase 3 trials of the SURPASS development programme in patients with T2DM (see Table 1). In addition to its glucose-lowering action, tirzepatide (5, 10, and 15 mg) caused a marked weight loss in patients with T2DM and various antihyperglycaemic background medications (see Table 2).

Table 1 Phase 3 trials of the SURPASS development programme

Study	Duration [weeks]	Comparator	Design	Antihyperglycaemic background medication
SURPASS-1	40	Placebo	Double-blind	None
SURPASS-2	40	Semaglutide	Open-label	Metformin
SURPASS-3	52	Insulin Degludec	Open-label	Metformin ± SGLT2i
SURPASS-4	104	Insulin Glargine	Open-label	Metformin ± SU ± SGLT2i
SURPASS-5	40	Placebo	Double-blind	Insulin glargine ± Metformin

SGLT2i, SGLT2 inhibitor SU, sulphonylurea

Table 2 Efficacy outcomes of the SURPASS development programme

Study	Comparator	TZP dose	Mean treatment difference [95% CI] for the treatment-regimen estimand	
			ΔA1C (%)	ΔBW (kg)
SURPASS-1	Placebo	5 mg 10 mg 15 mg	-1.66 [-1.96, -1.36] -1,62 [-1.92, -1.32] -1.60 [-1.91, -1.30]	-5.3 [-6.8, -3.9] -6.0 [-7.4, -4.6] -6.8 [-8.3, -5.4]
SURPASS-2	Semaglutide	5 mg 10 mg 15 mg	-0.15 [-0.28, -0.03] -0.39 [-0.51, -0.26] -0.45 [-0.57, -0.32]	-1.9 [-2.8, -1.0] -3.6 [-4.5, -2.7] -5.5 [-6.4, -4.6]
SURPASS-3	Insulin Degludec	5 mg 10 mg 15 mg	-0.60 [-0.74, -0.45] -0.76 [-0.90, -0.61] -0.89 [-1.03, -0.74]	-8.9 [-10.0, -7.8] -11.5 [-12.6, -10.4] -13.2 [-14.3, -12.1]
SURPASS-4	Insulin Glargin	5 mg 10 mg 15 mg	-0.72 [-0.86, -0.58] -0.91 [-1.05, -0.77] -1.02 [-1.15, -0.89]	-8.1 [-8.9, -7.3] -10.6 [-11.4, -9.8] -12.2 [-13.0, -11.5]
SURPASS-5	Placebo	5 mg 10 mg 15 mg	-1.24 [-1.48, -1.01] -1.53 [-1.77, -1.30] -1.47 [-1.71, -1.23]	-19.0 [-26.6, -11.4] -24.9 [-32.3, -17.4] -23.4 [-31.0, -15.8]

As illustrated further below (see Figure 1 and Figure 2 taken from Clinical Overview Figures 2.5.4.1 and 2.5.4.4), 2 dedicated placebo-controlled Phase 3 trials (SURMOUNT-1 and SURMOUNT-2) provided compelling proof of weight-reducing efficacy in patient populations with obesity/overweight representative of the target population requested (see Table 3 taken from the Clinical Overview Table 2.5.4.1).

The doses and dose-escalation scheme used in the SURMOUNT-1 and SURMOUNT-2 trials were selected based on assessment of safety, efficacy (weight reduction and glycaemic control), and GI tolerability data from the Phase 2 studies, exposure-response modelling of data from participants with T2DM in Phase 1 and 2 studies, and the model prediction for participants without T2DM with obesity (see Table 4 taken from Clinical Overview Table 2.5.4.2).

Table 3. Key design features for SURMOUNT-1 and SURMOUNT-2

Design Elements	I8F-MC-GPHK SURMOUNT-1	I8F-MC-GPHL SURMOUNT-2
Participant Population	Participants with obesity, or overweight with at least 1 weight-related comorbid condition, without diabetes	Participants with obesity or overweight and T2DM
Comparator	Placebo	
Randomization	1:1:1:1 (TZP 5 mg: TZP 10 mg: TZP 15 mg: PBO)	1:1:1 (TZP 10 mg: TZP 15 mg: PBO)
Treatment Duration	72 weeks[a]	72 weeks
Primary Endpoint	• Mean percent change in body weight • Proportion of participants who achieved ≥5% body weight reduction	
Blinding	Double-blind	
Trial Size (N)	2539[a]	938
Countries that Enrolled Participants	Argentina, Brazil, China, India, Japan, Mexico, Russian Federation, Taiwan, and United States	Argentina, Brazil, India, Japan, Russian Federation, Taiwan, and United States

TZB = Tirzepatide; PBO = Placebo

Table 4 Tirzepatide dose-escalation scheme in the Phase 3 studies

Treatment Group	Treatment Period Intervals					
	Weeks 0 to 4	Weeks 4 to 8	Weeks 8 to 12	Weeks 12 to 16	Weeks 16 to 20	Week 20 through End of Treatment Period
Tirzepatide 5 mg	2.5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Tirzepatide 10 mg	2.5 mg	5 mg	7.5 mg	10 mg	10 mg	10 mg
Tirzepatide 15 mg	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg

Figure 1 SURMOUNT-1 efficacy outcomes

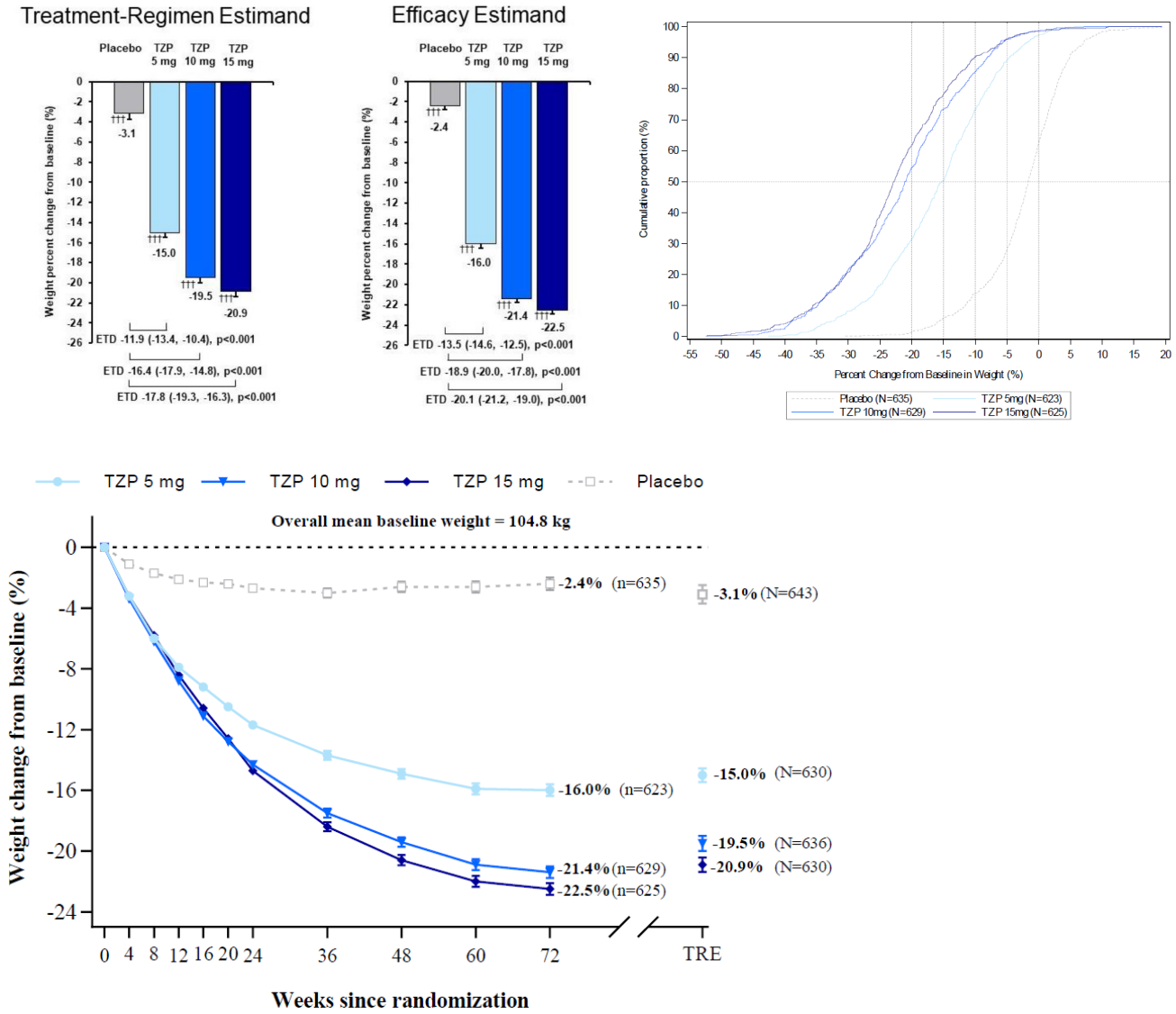
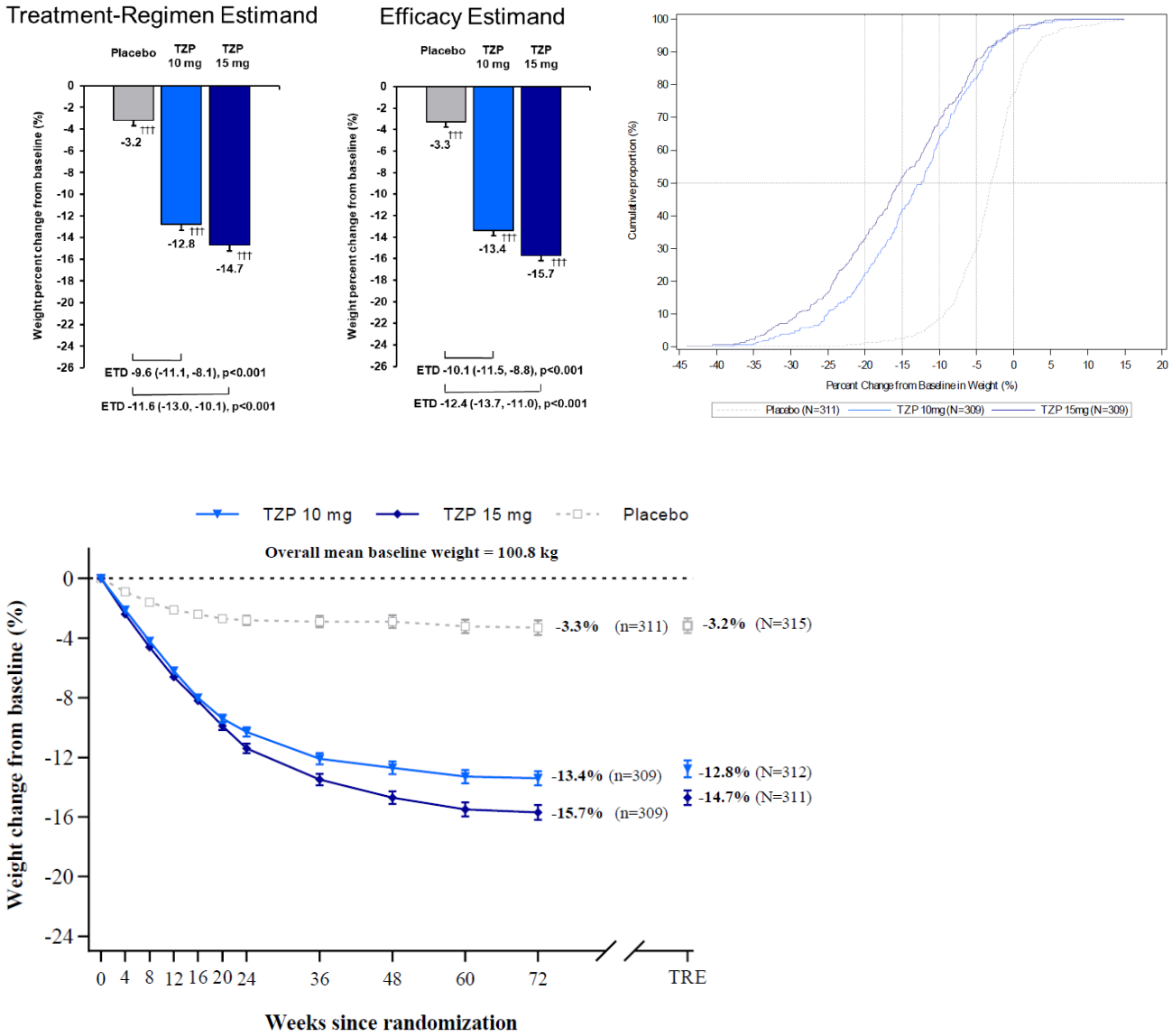


Figure 2 SURMOUNT-2 efficacy outcomes



5.3 Safety

The safety profile of tirzepatide has been well characterised in the SURPASS programme for initial approval in patients with T2DM, a population that overlaps with the target population of the present application. Tirzepatide's safety profile in the SURPASS studies largely resembled that of GLP1RAs (glucagon-like peptide 1 receptor agonists), and no additional safety concerns specifically related to the dual agonism were observed.

The safety profile in the 2 SURMOUNT studies supporting the present application for chronic weight management confirmed that previously observed in the SURPASS programme. The SURMOUNT trials identified no new clinically relevant safety concerns.

5.4 Final clinical benefit-risk assessment

Beneficial effects and respective uncertainties

The effect of tirzepatide on gastric emptying using paracetamol PK as a pharmacodynamic endpoint in overweight/obese non-diabetic and overweight/obese T2DM subjects was comparable to the results for T2DM patients in the primary application.

There were no major differences in tirzepatide exposures between overweight/obese subjects without T2DM and T2DM patients.

Tirzepatide caused dose/concentration-dependent weight loss, predominantly due to a reduction in fat mass rather than fat-free mass in overweight/obese subjects without T2DM.

In the pivotal studies, tirzepatide induced sustained and pronounced weight loss in a broad patient population representing the target population. The weight loss observed was more pronounced in non-T2DM subjects than in T2DM subjects (average weight reduction with tirzepatide 15 mg: 22.5% vs. 15.7%).

Undesirable effects and respective uncertainties

The safety profile of tirzepatide in the pivotal trial largely resembled that of GLP1Ras, with gastro-intestinal adverse events dominating. These AEs could be partially, but not completely, eliminated by careful dose titration.

Benefit-risk assessment

The benefit-risk ratio is considered positive due to convincing proof of efficacy and a generally manageable safety profile with no unexpected, prohibitive safety signals.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Mounjaro was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼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 new or serious adverse reactions. Instructions for reporting side effects, see section "Undesirable effects".

MOUNJARO®

Composition

Active ingredients

Tirzepatide

List of excipients

Sodium monohydrogen phosphate heptahydrate
Sodium chloride
Hydrochloric acid and sodium hydroxide (for pH adjustment)
Water for injections
Total sodium content: 1.8-1.9 mg/0.5ml

Pharmaceutical form and active substance quantity per unit

Solution for injection in a pre-filled pen.

Each single use pre-filled pen contains 2.5mg, 5mg, 7.5mg, 10mg, 12.5mg or 15mg resp. of tirzepatide in 0.5 ml solution.

Solution for injection in vial.

Each single use vial contains 2.5mg, 5mg, 7.5mg, 10mg, 12.5mg or 15mg resp. of tirzepatide in 0.5 ml solution.

Indications/Uses

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 contraindicated or not tolerated;
- in combination with other drugs that lower blood glucose.

See "Clinical efficacy" section for results on the combinations examined in clinical studies.

Chronic weight management

Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic 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 < 30kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnoea, cardiovascular disease, prediabetes or type 2 diabetes mellitus).

Dosage/Administration

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 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 sulphonyl urea or insulin, a reduction in the dose of sulphonyl urea or insulin should be considered to reduce the risk of hypoglycemia. Blood glucose self-monitoring is necessary to adjust the dose of sulphonyl urea and insulin. A stepwise approach to insulin reduction is recommended.

The day of weekly administration can be changed, if necessary, as long as the last dose had been administered at least 3 days (72 hours) before.

Specific dose instructions (see also section "Pharmacokinetics")

No dose adjustment is needed based gender, race, ethnicity, and body weight.

Elderly patients

No dose adjustment is needed.

Patients with Renal impairment

No dose adjustment is needed including end stage renal disease.

Patients with Liver impairment

No dose adjustment is needed.

Children and adolescents

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

Delayed 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 next regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

Type 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.

Rotate injection sites with each dose.

Patients should be advised to carefully read the instructions for use included with the package leaflet for the pre-filled pen or the „Instructions for use/handling“” in the package leaflet for the vial before administering the medicinal product.

Contraindications

Hypersensitivity to the active substance or to any of the excipients

Warnings and Precautions

Patients with medullary thyroid carcinoma

Studies with GLP-1 receptor agonists and tirzepatide in rodents show an increased risk of thyroid C-cell tumours (see section "Preclinical data"). An analogous increase in the risk of thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans is unclear. Patients with MTC or multiple endocrine neoplasia syndrome type 2 (MEN 2) have not been studied in clinical trials with tirzepatide. These patients should therefore only be treated with tirzepatide after a careful risk/benefit evaluation.

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

Hypoglycaemia

Patients receiving tirzepatide in combination with a sulphonyl urea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of sulphonyl urea or insulin, respectively.

Gastrointestinal effects

Tirzepatide has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhoea. These events may lead to dehydration, which could lead to deterioration in renal function including acute renal failure. Patients treated with tirzepatide, in particular patients with impaired renal function, should be advised of this and take precautions to avoid fluid depletion.

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

In patients with non-proliferative diabetic retinopathy requiring acute therapy, and in patients with proliferative diabetic retinopathy or diabetic macular oedema, Tirzepatide should be used with caution and related monitoring. A too quick or too strong reduction in blood glucose values, particularly in patients with diabetic retinopathy, could initially trigger a deterioration of that condition.

Acute diseases of the gallbladder

Clinical trial results and post-marketing data for GLP-1 receptor agonists suggest an increased risk of acute gallbladder disease. In the placebo-controlled clinical trials of the tirzepatide development program, such events (cholelithiasis, biliary colic and cholecystectomy) occurred in 0.6% of tirzepatide-treated patients, while no (0%) cases were reported in the placebo control. If cholelithiasis is suspected, careful diagnostic clarification and appropriate follow-up checks are indicated.

Sodium content

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

Interactions

Tirzepatide delays gastric emptying, as assessed by paracetamol pharmacokinetics, and thereby has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. This requires particular consideration when medicinal products whose efficacy depends on threshold concentrations are administered simultaneously with tirzepatide and for those with a narrow therapeutic window (for instance warfarin, digoxin).

Based on physiologically-based pharmacokinetic models, it is not anticipated that tirzepatide treatment will result in a clinically meaningful impact on orally administered medicinal products (i.e., warfarin, metformin, lisinopril, metoprolol, digoxin, paracetamol, norelgestromin, ethinylestradiol, sitagliptin, and atorvastatin). No dosage adjustments of concomitantly administered oral medicinal products are required.

Paracetamol

Following a single dose of tirzepatide 5 mg, paracetamol maximum concentration (C_{max}) was reduced by 50 %, and the mean peak plasma concentration (t_{max}) occurred 1 hour later. After coadministration at week 4, there was no meaningful impact on paracetamol C_{max} and t_{max}. Overall paracetamol exposure (AUC) was not influenced. No dose adjustment of paracetamol is necessary when administered with tirzepatide.

Oral contraceptives

Administration of combination oral contraceptives (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 contraceptives' 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.

Use of tirzepatide may reduce the efficacy of oral hormonal contraceptives. When using oral hormonal contraceptives, a switch to non-oral method of contraception is recommended, or to add a barrier method for at least 4 weeks after initiation of treatment with tirzepatide or after any increase in dose, respectively.

Pregnancy, lactation

Pregnancy

There are no or only limited amount of data for the use of tirzepatide in pregnant women. Experimental studies in animals have shown reproductive toxicity (see “Preclinical data”). Tirzepatide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with tirzepatide. Tirzepatide should not be used for weight reduction during pregnancy.

Breast-feeding

It is unknown whether tirzepatide is excreted in human milk. A risk to the breastfed child 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. There were indirect effects on fertility in female rats (see “Preclinical data”).

Effects on ability to drive and use machines

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

Undesirable effects

Summary of safety profile

Type 2 diabetes mellitus

In 7 completed phase 3 studies, 5 119 patients have received 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, diarrhoea and vomiting. In general, these reactions were mostly mild or moderate in severity and occurred more often during dose escalation and decreased over time.

Chronic weight management

In 2 completed phase 3 studies, 2519 patients were exposed to tirzepatide alone or in combination with other glucose lowering medicinal products. The most frequently reported adverse reactions were gastrointestinal disorders, including nausea (very common), diarrhoea (very common), constipation (very common), and vomiting (very common). In general, these reactions were mostly mild or moderate in severity and occurred more often during dose escalation and decreased over time.

List of adverse reactions

The evaluation of clinical studies resulted in the following adverse reactions that are listed in MedDRA terminology 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).

Immune system disorders

Common: Hypersensitivity reactions

Nervous system disorders

Common: Dizziness[d]

Vascular disorders

Common: Hypotension[d]

Gastrointestinal disorders

Very common: Nausea (18 -28%), diarrhoea (15-21 %), constipation[d] (13.6%), vomiting[d] (10.8%)
Common: abdominal pain, vomiting[a], dyspepsia, constipation[a], meteorism, eructation, flatulence, gastroesophageal reflux disease

Metabolism and nutrition disorders

Common: decreased appetite[a]

Hypoglycemia in patients with type 2 Diabetes[b]

Very common:
Hypoglycaemia[b] when used with sulfonylurea or insulin:

- with sulphonyl urea (10-14 %).
- with basal insulin (14-19 %).

Common:

Hypoglycaemia[b] when used with metformin and SGLT2i[c,]

Uncommon:

Hypoglycaemia[b] when used with metformin

Skin and subcutaneous tissue disorders

Common: Hair loss[d]

General disorders and administration site conditions

Common: Fatigue, injection site reactions.

[a] Type 2 diabetes mellitus indication only

[b] Clinically significant hypoglycaemia was defined as blood glucose <3.0 mmol/L (<54 mg/dL) or severe hypoglycaemia (requiring the assistance of another person)

[c] Sodium-glucose co-transporter inhibitor

[d] Chronic weight management indication only

The following adverse drug reactions are based on postmarketing reports of tirzepatide.

Rare: Anaphylactic reaction and angioedema

Description of selected adverse reactions and additional information

Hypersensitivity reactions

Hypersensitivity reactions to tirzepatide have been reported in the pool of T2DM placebo-controlled trials. The reactions were occasionally serious (for example, urticaria and eczema). Hypersensitivity reactions have been reported in 3.2% of patients who were treated with tirzepatide and in 1.7% of patients who were given a placebo

Hypersensitivity reactions have been reported with tirzepatide in the pool of chronic weight management placebo-controlled trials, sometimes severe (e.g., dermatitis and rash); hypersensitivity reactions were reported in 5.1 % of tirzepatide-treated patients compared to 3.1 % of placebo-treated patients.

Hypoglycemia in patients with type 2 diabetes

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

Clinically significant hypoglycemia occurred in 10 to 14 % (0.14 to 0.16 events/patient year) of patients when tirzepatide was added to sulphonyl urea 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 hypoglycemia when tirzepatide was used as monotherapy or when added to other oral antidiabetic medicinal products was up to 0.03 events/patient year.

Gastrointestinal adverse reactions

Gastrointestinal events were mostly mild or moderate in severity. The incidence of nausea, vomiting, and diarrhea was higher during the dose escalation period and decreased over time.

Immunogenicity

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

Diabetes mellitus Type 2

Across seven Phase 3 clinical studies, 2 570 (51.1 %) tirzepatide-treated patients developed ADA. In these trials, ADA formation in 34% and 14% of tirzepatide-treated patients showed cross-reactivity to native glucose-dependent insulinotropic polypeptide (GIP) or native GLP-1, respectively.

Of the 2 570 tirzepatide-treated patients, 1.9 % and 2.1 % had neutralizing antibodies against tirzepatide activity on the GIP and 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 associated with the development of ADA.

More tirzepatide-treated patients who developed anti-tirzepatide antibodies experienced hypersensitivity reactions or injection site reactions than those who did not develop these antibodies.

Chronic weight management

Across two Phase 3 clinical studies, 64.5% of tirzepatide-treated patients with obesity or overweight developed ADAs. Of the overall tirzepatide-treated patients with obesity or overweight, 2.8% and 2.7% had neutralizing antibodies against tirzepatide activity on the GIP

and GLP-1 receptors, respectively. 0.8% and 0.1% had neutralizing antibodies against native GIP and GLP-1 respectively.

Reporting suspected adverse reactions after authorization 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 new or serious adverse reaction through the online portalElViS (ElectronicVigilance System). Information on this can be found at www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code

A10BX16

Mechanism of action

Diabetes mellitus type 2 and Chronic Weight Management

Tirzepatide is a long-acting GIP and GLP-1 receptor agonist. It is a 39-amino acid peptide with a C20 fatty diacid moiety that enables albumin binding and prolongs half-life.

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

Tirzepatide improves insulin sensitivity.

Tirzepatide decreases food intake.

Diabetes mellitus type 2

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

Tirzepatide delays gastric emptying, and this effect diminishes over time.

Chronic Weight Management

Both GIP-R and GLP-1 R are found in areas of the brain important for appetite regulation.

Tirzepatide regulates appetite and decreases food intake. Tirzepatide lowers body weight and body fat mass.

An animal study showed that tirzepatide modulates energy expenditure.

Pharmacodynamics

Glycemic control

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

Fasting serum glucose

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

Postprandial glucose

Treatment with tirzepatide resulted in significant reductions in mean post prandial glucose concentration 2 hours after administration (mean of the 3 meals per day) from baseline (changes from baseline to final value were -3.35 mmol/L to -4.85 mmol/L).

Insulin Secretion

In a hyperglycemic 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 and the rates increased for semaglutide 1 mg by 298 % and 223 %, respectively.

Insulin Sensitivity

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

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

Gastric Emptying

Tirzepatide delays gastric emptying which may slow post meal glucose absorption and can lead to a beneficial effect on postprandial glycaemia. Tirzepatide slows post-meal glucose absorption, reducing postprandial glucose. The delay is largest after the first dose and this effect diminishes over time. The reduction of the postprandial glucose levels was more pronounced in subjects with T2DM compared to subjects with obesity or overweight without T2DM.

Pancreatic enzymes

Type 2 diabetes mellitus

In the placebo-controlled phase 3 studies, treatment with tirzepatide resulted in mean increases from baseline in pancreatic amylase of 33 % to 38 % and lipase of 31 % to 42 %. Placebo treated patients had an increase from baseline in amylase of 4 % and no changes were observed in lipase. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis

Chronic weight management

Treatment with tirzepatide resulted in mean increases from baseline in pancreatic amylase of 20% to 25% and lipase of 28% to 35%.

Cardiac electrophysiology (QTc intervals)

Tirzepatide does not prolong QTc intervals at doses of up to 15 mg.

Clinical efficacy

Type 2 diabetes mellitus

Glycemic control and body weight

The safety and efficacy of tirzepatide were analysed in five global randomized, controlled, phase 3 studies (SURPASS 1-5), which included a total of 6263 patients with type 2 diabetes,

4199 of whom were treated with tirzepatide. The primary endpoint for evidence of glycaemic efficacy was the change (reduction) in HbA1c. Significant secondary endpoints were the change (reduction) in body weight and the fasting serum glucose (FSG) as well as the percentage of patients who achieved the HbA1c target level (responder rate). All the studies analysed tirzepatide 5, 10 and 15 mg and the following titration plan was used. The initial dose was 2.5 mg a week and it was increased by 2.5 mg every 4 weeks until the assigned target dose was reached (5, 10 or 15 mg).

Compared to the comparator arm (placebo, semaglutide, insulin degludec or insulin glargine) treatment with tirzepatide demonstrated in all the studies a superior reduction of HbA1c and body weight during a period of treatment from 40 – 104 weeks. The results of the individual studies are described in detail below, based on a modified intent-to-treat (mITT) population (all randomised patients who received ≥ 1 dose of the study medication, apart from those patients who terminated the treatment due to inadvertent enrolment). A mixed model for repeated measurements was used to assess efficacy.

SURPASS 1 – Monotherapy

In a 40-week double blind placebo-controlled study, 478 patients (average age at baseline ~54 years) with inadequate glycaemic control with diet and exercise (average HbA1c at baseline ~7.94%), were randomised to tirzepatide 5 mg, 10 mg, or 15 mg once weekly or placebo. At baseline the patients had a mean duration of diabetes of approx. 4.7 years.

Table 1. 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
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]	-

* 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.

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. At baseline the patients had a mean duration of diabetes of 9 years.

Table 2. 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
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]	-

* $p < 0.05$, **$p < 0.001$ 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.

SURPASS 3 – In combination 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. 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. At baseline the patients had a mean duration of diabetes of 8 years.

Table 3. SURPASS 3: Results at week 52

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Titrated insulin degludec[a]
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
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]	-

[a] The mean dose of insulin degludec at week 52 was 49 units/day.

* 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.

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 euglycemic 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.

At 52 weeks patients in all 3 tirzepatide dose groups spent a greater proportion of the 24-hour period with blood glucose in the range of 71 to 180 mg/dL (3.9 to 10.0 mmol/L) than patients treated with insulin degludec: tirzepatide (range), 84.9 % to 91.2 %; insulin degludec, 75.0 %.

Liver fat content (LFC) and adipose tissue

A subset of patients (N = 296) participated in an evaluation of LFC, visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (ASAT) assessed through magnetic resonance imaging. At 52 weeks, patients treated with tirzepatide (10 mg and 15 mg pooled) demonstrated statistically significantly greater mean reductions in LFC compared to insulin

degludec, -8.09 % versus -3.38 % respectively, from baselines of 15.67 % and 16.58 %. Patients treated with tirzepatide 5 mg, 10 mg and 15 mg had significantly greater reductions in volume of VAT (-1.10, -1.53 and -1.65 L respectively) and ASAT (-1.40, -2.25 and -2.05 L respectively) from overall baselines of 6.6 L and 10.4 L respectively at 52 weeks compared with an increase in the insulin degludec group (0.38 and 0.63 L).

SURPASS 4 – In combination with 1-3 oral antidiabetic medicinal products (metformin, sulphonyl ureas 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 sulphonyl ureas (54 %) and/or SGLT2i (25 %). Patient 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. At baseline the patients had a mean duration of diabetes of 12 years.

Table 4. SURPASS 4: Results at week 52

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Titrated insulin glargine[a]
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
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]	-

[a] The mean dose of insulin glargine at week 52 was 44 units/day.

* $p < 0.05$, ** $p < 0.001$ 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.

SURPASS 5 - In combination with basal insulin, with or without metformin

In a 40-week double-blind placebo-controlled study, 475 patients with inadequate glycemic control using insulin glargine with or without metformin were randomized 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. For patients with HbA1c ≤8.0% the insulin glargine dose was reduced by 20% during the first week (until administration of the second Tirzepatide dose). For patients with baseline HbA1c >8.0%, the insulin glargine dose was not decreased. At baseline the patients had a mean duration of diabetes of 13 years.

Table 5. SURPASS 5: Results at week 40

		Tirzepatide 5 mg	**Tirzepatide 10 mg**	**Tirzepatide 15 mg**	**Placebo[a]**
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
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]	-

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

[*] p < 0.05, **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.

Chronic weight management

The safety and efficacy of tirzepatide for chronic weight management (weight reduction and maintenance) in combination with a reduced calorie intake and increased physical activity

were evaluated in two randomized double-blinded, placebo-controlled phase 3 studies in patients without diabetes mellitus (SURMOUNT-1) and with diabetes mellitus (SURMOUNT-2).

SURMOUNT-1

In a 72 week double blind placebo-controlled study, 2 539 adult patients (67.5% women) 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 with manifest type 2 diabetes mellitus were excluded. However, 40.6% of the study participants had prediabetes. Patients had a mean age of 45 years. Mean baseline body weight was 104.8 kg and mean BMI was 38 kg/m^2.

In SURMOUNT-1 the dose of tirzepatide or matching placebo was escalated to 5 mg, 10 mg, or 15 mg subcutaneously once weekly during a 20-week period followed by the maintenance period.

Weight loss with tirzepatide occurred early and continued throughout the trial. At end of treatment (week 72), the weight loss with tirzepatide was superior and clinically meaningful compared with placebo (see table 7. and figure 6.). 89%, 96%, and 96% of patients in the 5 mg, 10 mg, and 15 mg tirzepatide groups, respectively, had a body weight reduction of ≥5%at 72 weeks, as compared with 28% of patients in the placebo group (P<0.001 for all comparisons with placebo). More patients in the tirzepatide groups had reductions in body weight of ≥10%, ≥15%, and ≥20% from baseline than patients in the placebo group (P<0.001).

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 value < 0.001 versus placebo, not adjusted for multiplicity.

**p value < 0.001 versus placebo, adjusted for multiplicity.

††p value < 0.001 versus baseline.

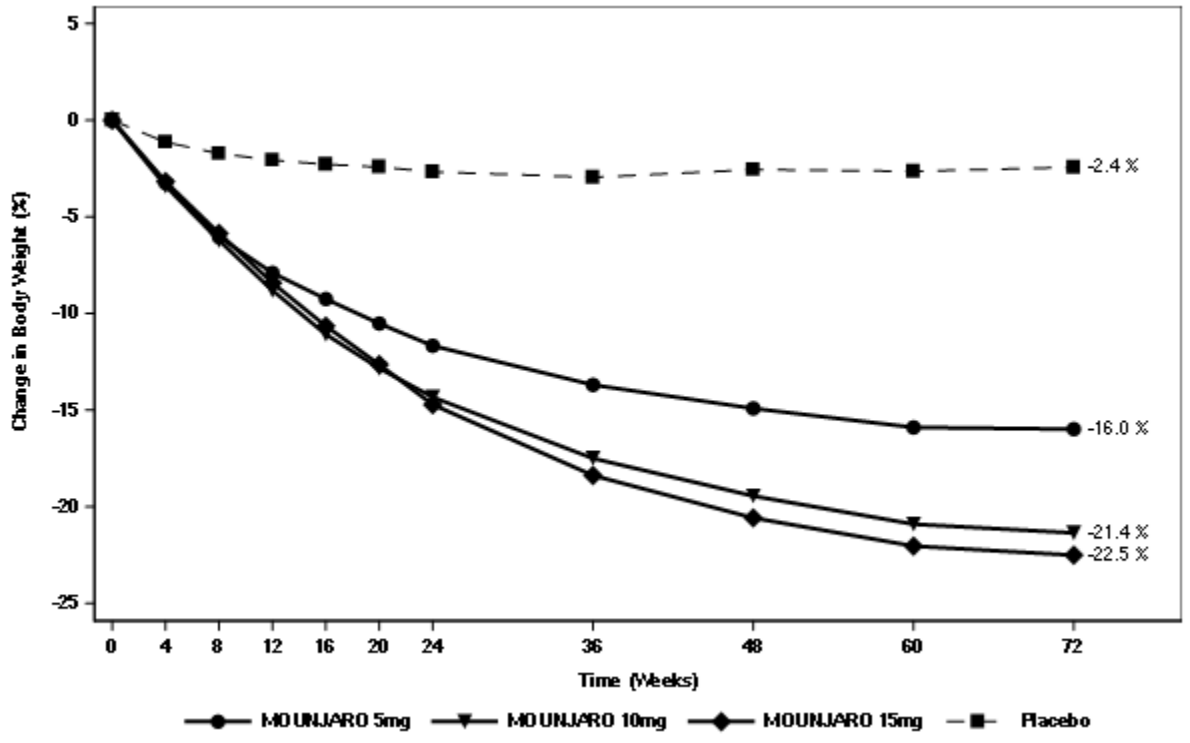


Figure 6. Mean change in body weight (%) from baseline to week 72

In the subgroup with prediabetes at baseline (N = 1032), 95.3 % patients treated with tirzepatide reverted to normoglycemia at week 72, compared to 61.9 % of patients on placebo treatment.

SURMOUNT-2

In a 72-week double blind placebo-controlled study, 938 adult patients with BMI ≥27 kg/m^2 and type 2 diabetes mellitus, were randomised to tirzepatide 10 mg or 15 mg once weekly or placebo. Patients had a mean age of 54 years and 50.7 % were women. Mean baseline body weight was 100.7 kg and mean BMI was 36.1 kg/m^2.

The dose of tirzepatide or matching placebo was escalated to 10 mg or 15 mg subcutaneously once weekly during a 20-week period followed by the maintenance period.

Weight loss occurred early and continued throughout the trial. At end of treatment (week 72), the weight loss was superior and clinically meaningful compared with placebo (see table 8 and figure 7). 81.6% and 86.4% of patients in the 10 mg, and 15 mg tirzepatide groups, respectively, had a body weight reduction of 5% or more at 72 weeks, as compared with 30.6% of patients in the placebo group (P<0.001 for all comparisons with placebo). More patients in the tirzepatide groups had reductions in body weight of 10% or more, 15% or more, and 20% or more from baseline than patients in the placebo group (P<0.001).

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**	30.6
≥ 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]	-

[##]p value < 0.001 versus placebo, not adjusted for multiplicity.

**p value < 0.001 versus placebo, adjusted for multiplicity.

[††]p value < 0.001 versus baseline.

During the trial, treatment was permanently discontinued by 9.3 % and 13.8 % of patients randomised to tirzepatide 10 mg and 15 mg respectively compared to 14.9 % randomised to placebo.

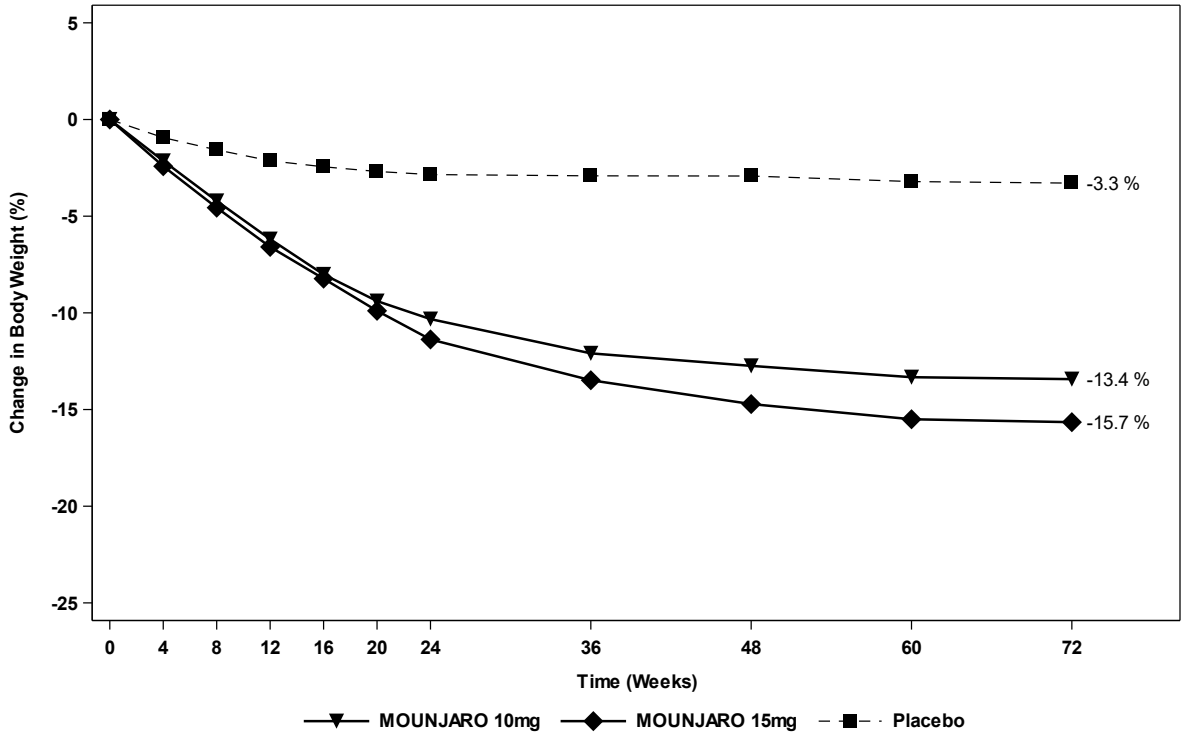


Figure 7. Mean change in body weight (%) from baseline to week 72

Other information

Changes in 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.

Cardiovascular Evaluation

Diabetes mellitus type 2

Cardiovascular (CV) risk was assessed via a meta-analysis of phase 2 and phase 3 studies. The composite endpoint (major cardiac event, MACE-4) included CV death, nonfatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina. All the events that occurred were adjudicated by a panel of cardiologists.

In a primary meta-analysis, 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).

Chronic weight management

An analysis was conducted for the SURMOUNT-1 study where a total of 14 patients (tirzepatide: 9 (0.47 %) out of 1 896; placebo: 5 (0.78 %) out of 643) experienced at least one adjudication confirmed MACE. Percentages of patients with adjudication confirmed MACE were similar across placebo and tirzepatide groups.

Analysis was conducted for the SURMOUNT-2 study. A total of 11 patients (tirzepatide: 7 (1.12 %) out of 623 placebo: 4 (1.27 %) out of 315) experienced at least one adjudication confirmed MACE. Percentages of patients with adjudication confirmed MACE were similar across placebo and tirzepatide groups.

Blood Pressure

Diabetes mellitus type 2

In the placebo-controlled phase 3 studies, 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.

Chronic weight management

Treatment with tirzepatide resulted in a mean decrease in systolic and diastolic blood pressure of 7 to 8 mmHg and 4 to 5 mmHg, respectively. There was a mean decrease in systolic and diastolic blood pressure of 1 mmHg each in placebo-treated patients.

Heart Rate

Diabetes mellitus Type 2

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 patients receiving placebo.

Chronic weight management

Treatment with tirzepatide resulted in a mean increase in heart rate of 1 to 3 beats per minute. There was a mean increase in heart rate of 0 beats per minute in placebo-treated patients.

Special populations

The efficacy of tirzepatide for treatment of diabetes mellitus type 2 was not impacted by age, gender, race, ethnicity, region, or by baseline BMI, HbA1c, diabetes duration and level of liver or renal function impairment.

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

Pharmacokinetics

Absorption

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

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

Absolute bioavailability of subcutaneous tirzepatide was 80 %.

Distribution

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

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

Metabolism

Tirzepatide is metabolized 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 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 feces. Intact tirzepatide is not observed in urine or feces.

Kinetics in special populations

Age, gender, race, ethnicity

Age, gender, race, or ethnicity do not have a clinically relevant effect on the pharmacokinetics (PK) of tirzepatide. Assessment originates from a population pharmacokinetic analysis.

Patients with Type 2 Diabetes mellitus

Tirzepatide PK are similar in individuals with T2DM compared to individuals with obesity or overweight without T2DM.

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.

Renal impairment

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

Elderly patients

Age had no clinically relevant effect on the pharmacokinetic and pharmacodynamic properties of tirzepatide

Children and adolescents

Tirzepatide has not been studied in pediatric patients.

Body weight

Pharmacokinetic analyses have described an inverse relationship between body weight and tirzepatide exposure, although there was no clinically relevant effect of weight on glycemic control.

Preclinical data

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

Carcinogenicity

A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.12, 0.36, and 1.02-fold the maximum recommended human dose (MRHD) based on AUC administered by subcutaneous injection twice weekly. Tirzepatide caused an increase in thyroid C-cell tumors (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 (1.2, 3.4, and 10.6-fold of the weekly recommended maximum dose in human (MRHD) based on AUC) administered by subcutaneous injection twice weekly did not produce increased incidences of neoplasia at any dose.

Reproduction toxicity

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

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

In reproduction studies, an increased incidence of external, visceral, and skeletal malformations and visceral and skeletal developmental variations were observed in rats. In rats and rabbits, fetal growth reductions were observed. All developmental effects occurred at maternal toxic doses. The animal's exposure was below the MRHD based on AUC. In juvenile animal studies, consistent with studies in adult rats, effects of tirzepatide on growth and

development in juvenile animals were limited to pharmacological effects on body weight and food consumption. Delays in the balanopreputial separation and vaginal patency were noted for males and females, which was attributed to the tirzepatide-related effects on body weight and not considered a direct result of tirzepatide.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special storage instructions

Store in a refrigerator (2 ºC – 8 ºC).

Do not freeze.

Store in original package in order to protect from light.

Temporary storage

Mounjaro may be stored unrefrigerated for up to 21 days at a temperature not above 30 ºC.

Keep out of reach of children.

Information on handling

Pre filled pen:

The pre-filled pen is for single-use only.
The instructions for using the pen, contained in the package must be followed carefully.
Inspect Mounjaro visually before use and discard for particulate matter or discoloration.
Mounjaro that has been frozen must not be used.

Vial:

The vial is for single-use only.
The instructions how to inject Mounjaro from a vial, included in the package leaflet, must be followed carefully.
Inspect Mounjaro visually before use and discard for particulate matter or discolouration.
Mounjaro that has been frozen must not be used.

Authorization number

68726, 69415 (Swissmedic)

Packs

Mounjaro 2.5 mg solution for injection in a single-dose pre-filled pen:4 pens (B)

Mounjaro 5 mg solution for injection in a single-dose pre-filled pen:4 pens (B)

Mounjaro 7.5 mg solution for injection in a single-dose pre-filled pen:4 pens (B)

Mounjaro 10 mg solution for injection in a single-dose pre-filled pen:4 pens (B)

Mounjaro 12.5 mg solution for injection in a single-dose pre-filled pen:4 pens (B)

Mounjaro 15 mg solution for injection in a single-dose pre-filled pen:4 pens (B)

Mounjaro 2.5 mg solution for injection in a single-use vial: 1 vial and 4 vials (B)

Mounjaro 5 mg solution for injection in a single-use vial: 1 vial and 4 vials (B)

Mounjaro 7.5 mg solution for injection in a single-use vial: 1 vial and 4 vials (B)

Mounjaro 10 mg solution for injection in a single-use vial: 1 vial and 4 vials (B)

Mounjaro 12.5 mg solution for injection in a single-use vial: 1 vial and 4 vials (B)

Mounjaro 15 mg solution for injection in a single-use vial: 1 vial and 4 vials (B)

Marketing authorization holder

Eli Lilly (Suisse) S.A., Vernier / Genève

Date of revision of the text

April 2024