Date: 3 February 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

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: approved on 2 November 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
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
CK	Creatine kinase
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 efficacy
ERA	Environmental Risk Assessment
ESRD	End-stage renal disease
FDA	Food and Drug Administration (USA)
GE	Gastric emptying
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GLP	Good Laboratory Practice
GLP-1	Glucagon-like peptide 1
GLP-1R	Glucagon-like peptide 1 receptor
HPLC	High performance liquid chromatography
HR	Hazard ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IDeg	Insulin degludec
Ig	Immunoglobulin
IGlar	Insulin glargine
INN	International nonproprietary name
ITT	Intention-to-treat
IV	Intravenous
kDa	Kilodalton
LoQ	List of Questions
LSM	Least square mean
MACE	Major adverse cardiac events
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTC	Medullary thyroid carcinoma
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
OAM	Oral anticancer medicine
OC	Oral contraceptive

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PBPK	Physiology-based pharmacokinetic
PD	Pharmacodynamics
PFS	prefilled syringe
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSP	Pediatric Study Plan (US-FDA)
QW	Once weekly
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous
SDP	Single-dose pen
SGLT2	Sodium/glucose cotransporter 2
SwissPAR	Swiss Public Assessment Report
TE ADA+	Treatment-emergent anti-drug antibody positive
TE ADA-	Treatment-emergent anti-drug antibody negative
TEAE	Treatment-emergent adverse event
T2DM	Type 2 diabetes mellitus
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
UACR	Urinary albumin/creatinine ratio

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance tirzepatide of the medicinal product mentioned above.

Work-sharing procedure
The applicant requested a work-sharing procedure with Canada.
The Access NAS (New Active Substance) work-sharing initiative is a collaboration between regulatory authorities, i.e. Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), Swissmedic, and the pharmaceutical industry.
The work-sharing initiative coordinates the assessment of an NAS application that has been filed in at least two jurisdictions.

2.2 Indication and Dosage

2.2.1 Requested Indication

Mounjaro is used to treat adults with type 2 diabetes mellitus in addition to diet and exercise.

2.2.2 Approved Indication

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.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
The initial dose of tirzepatide is 2.5 mg once a week. After 4 weeks, the dose is increased to 5 mg once a week. If necessary, the dose can be increased in increments of 2.5 mg after at least 4 weeks at the current dose. The maximum dose is 15 mg once a week.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	30 November 2021
Formal control completed	14 January 2022
List of Questions (LoQ)	13 May 2022
Answers to LoQ	11 July 2022
Predecision	25 August 2022
Answers to Predecision	11 September 2022
Final Decision	2 November 2022
Decision	approval

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3 Medical Context

Type 2 diabetes mellitus (T2DM) is a progressive disease typically requiring stepwise intensification of pharmacotherapy. There is a need for novel medications offering a robust and sustained glucose-lowering efficacy at different stages of the disease, preferably in combining benefits related to cardiovascular risk, kidney function or body weight control. In addition, slowing down or reversing progressive insulin resistance is desirable.

An emerging novel pharmacological strategy is to use so-called multi-agonists. The idea behind this concept is to merge the structural features of different members of the glucagon superfamily (glucagon-like peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP] and glucagon) into a single molecule. The three peptides have complementary actions which, if combined in one molecule, are expected to boost glucose lowering, weight reducing and other metabolic effects (e.g. hepatic lipid metabolism). Tirzepatide is a new 39 amino acid synthetic peptide based on the sequence of GLP-1 and GIP.

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4 Quality Aspects

Swissmedic has not assessed the primary data relating to quality aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

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5 Nonclinical Aspects

5.1 Pharmacology

Tirzepatide exerted a similar binding affinity to the glucose-dependent insulinotropic polypeptide receptor (GIPR) from human and monkey as native GIP, whereas its affinity for the rodent GIPR was 96-fold (rat) and 160-fold (mouse) lower. Tirzepatide's binding affinity to the glucagon-like peptide 1 receptor (GLP-1R) from human and monkey was 3- to 4-fold lower compared to native GLP-1, whereas the affinity to the rodent GLP-1R was similar to that of GLP-1.

In cell-based assays, tirzepatide's potency on the human GIPR was similar to native GIP, but it was a weaker agonist on the human GLP-1R. The maximum efficacy (E_{max}) of tirzepatide to activate the GLP-1R was about 50% the E_{max} of native GLP-1, whereas the E_{max} on GIPR was similar for tirzepatide and native GIP. Furthermore, tirzepatide did not elicit recruitment of β-arrestin-2 and internalisation of GLP-1R as native GLP-1, whereas the effects of tirzepatide on GIPR trafficking were similar to those induced by native GIP.

The presence of albumin in the *in vitro* experiments reduced the affinity and activity of tirzepatide. This is in line with the proposed albumin-binding properties of the fatty di-acid side chain connected to the peptide.

Tirzepatide enhanced *in vitro* glucose-dependent insulin secretion from rat and mouse pancreatic islets (EC_{50} 15.5 nM and 32 nM). In differentiated human adipocytes, tirzepatide stimulated cAMP production and lipolysis with higher potency than native GIP.

In vivo pharmacology studies in rats and mice showed efficacy of tirzepatide on glucose control by acting on both GIPR and GLP-1R, glucose-dependent insulin secretion, insulin sensitivity and body weight management in obese animals. In comparative studies using obese mice, tirzepatide demonstrated higher efficacy on reduction of food consumption, body weight loss and insulin sensitivity when compared to the selective GLP-1R agonist semaglutide (published in Samms *et al.*, 2021; doi: 10.1172/JCI146353). The results of these studies support the proposed use of tirzepatide in the treatment of T2DM.

Based on *in vitro* studies, tirzepatide has no relevant activity on the human glucagon receptor or glucagon-like peptide-2 receptor. Studies on secondary pharmacodynamics were not conducted, which was justified on the basis of the selectivity of tirzepatide for its target receptors and the lack of unexpected findings in the toxicity studies in pharmacologically relevant animals (see *Toxicology*).

Evaluation of safety pharmacology endpoints *in vitro* and *in vivo* did not reveal specific safety signals. Increased heart rate and decreased pulse pressure were observed in monkeys at relevant exposures. The investigators recorded similar observations in the clinical studies. Increased heart rate was also observed with other GLP-1R agonists. The GIPR expressed in the heart and the activity on this receptor may also contribute to the cardiovascular effects of tirzepatide.

5.2 Pharmacokinetics

The pharmacokinetics (PK) of tirzepatide following subcutaneous (SC) administration was adequately characterised in the animal species used for safety assessment. Bioavailability was similar in monkey (83%) and human (80%). Plasma T_{max} was 6 h in rats, 4-18 h in monkeys and 24 h in rabbits. Plasma half-life was shorter in rats (9 h), monkeys (56 h) and rabbits (45 h) when compared to humans (5 days). In the toxicity studies, exposure generally increased proportionally to dose, and accumulation was less than 2-fold, which is comparable to the PK of tirzepatide in the clinical studies. No sex-related differences in exposure were observed.

Tirzepatide bound *in vitro* highly to serum albumin from humans, rats and monkeys (≥99.7%); plasma protein binding was similar in humans and monkeys (99%), and slightly lower in rats (97.7%).

In single-dose studies with [^{14}C]tirzepatide in rats and monkeys, blood:plasma concentration ratios were <1, indicating no preferential distribution to blood cells. A quantitative whole-body autoradiography study in rats revealed wide tissue distribution, including in the brain.

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In vivo metabolism and excretion studies with [^{14}C]tirzepatide in rats and monkeys showed that tirzepatide was completely eliminated by metabolism in these species, as in humans. The metabolites identified in plasma and excreta were generated via proteolytic cleavage of the peptide backbone, β-oxidation of the C20 fatty acid moiety with and without taurine conjugation, and/or amide hydrolysis. The minor plasma metabolites identified in the human mass balance study were also present in plasma from the animal species. Drug-related material was excreted via urine and faeces; the profile in monkey (49% via urine, 35% via faeces) was similar to that in human.

Immunogenicity/ADA assessments were not included in the toxicity studies since there was no evidence of altered pharmacodynamic activity, changes in exposure or immune-mediated reactions. This is in line with ICH S6(R1). Results of quantitative cell-based assays indicate that active drug was present throughout the treatment period in the pivotal toxicity studies.

5.3 Toxicology

Rat and cynomolgus monkey served as main species for the toxicological assessment of tirzepatide based on the pharmacology data. Rabbit and mouse were the second species in reproductive toxicity or carcinogenicity testing. The species selection is considered adequate. Pharmacology-related effects (dose-limiting decreases in food consumption and body weight gain) occurred across species and studies. The clinical administration route (subcutaneous) was used in the studies; treatment was once weekly in monkeys and rabbits, and generally twice weekly in rats and mice, which accounts for the differences in $t_{1/2}$.

The duration of the long-term studies in rats and monkeys (6 months) supports the proposed chronic indication. Dose-related decreased food consumption and body weight gain or body weight loss occurred, which were associated with clinical signs (e.g., thin appearance or dehydration), changes in clinical pathology parameters, lower weights of several organs and several microscopic changes. The effects on food consumption and body weight reversed during recovery periods. Systemic exposure of animals at the highest doses in the chronic toxicity studies (3 mg/kg in rats and 0.5 mg/kg in monkeys), which were considered the NOAELs, was 1.3- to 2.0-fold the clinical AUC at the maximum recommended dose of 15 mg/week.

In line with ICH S6(R1), *in vitro* genotoxicity studies with tirzepatide were not conducted. In an *in vivo* bone marrow micronucleus assay in male rats, single SC administration of up to 3 mg/kg did not cause any effects. *In silico* assessment of the linker moiety revealed no alert for mutagenicity.

In the carcinogenicity study in rats, tirzepatide-related proliferative lesions and neoplastic findings were observed in the thyroid in both sexes at all dose levels (C-cell hyperplasia, adenoma and carcinoma). This is consistent with findings reported for other GLP-1R agonists (class effect). Thyroid C-cell tumours are considered an important potential risk (RMP). A respective warning note is included in the information for healthcare professionals. In the carcinogenicity study in transgenic RasH2 mice, there were no tirzepatide-related neoplastic findings or proliferative lesions (systemic exposure about 10.6-fold the clinical exposure at 15 mg/week).

In the fertility studies, treatment of female rats with tirzepatide led to increases in oestrus cycle length and decreased numbers of corpora lutea, implantation sites and viable embryos per litter. This was considered secondary to the effects on food consumption and body weight. The fertility study in male rats did not reveal tirzepatide-related effects on reproductive performance or sperm parameters.

In the embryofetal development (EFD) study in rats, the effects on food consumption and body weight gain in maternal animals were associated with increased post-implantation loss, lower fetal weights and increased incidences of fetal malformations and variations at exposures below the clinical exposure at the maximum recommended dose. Tirzepatide should not be used during pregnancy or in women of childbearing potential who do not use contraception; this is addressed in the information for healthcare professionals. In the EFD study in rabbits, mortality and abortions occurred at all dose levels, which was considered related to gastrointestinal lesions. These lesions were considered secondary to the pharmacological effects on gastrointestinal motility, for which rabbits are particularly

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sensitive. No adverse effects on embryofetal survival or development were observed in surviving maternal animals, but the tirzepatide exposure of the animals was below the clinical exposure.

In the pre- and postnatal development study in rats, treatment of maternal animals with tirzepatide had no effects on survival, development or reproductive function of the F1 generation except for reduced body weight gain in males. In the juvenile toxicity in rats conducted according to the EU-PIP, no adverse effects on development, neurobehavioural function or reproductive function were observed. Tirzepatide led to a delay in sexual maturity in male and female rats, which was attributed to the reduced body weight gain during treatment.

Local tolerance was evaluated in the repeat-dose studies. There were no findings indicative of local toxicity at the SC injection sites, in line with the low rates of local side reactions in the clinical studies.

Specific studies on immunotoxicity were not conducted and are not considered necessary since there were no relevant findings in the repeat-dose studies.

There are no concerns with regard to the excipients in the drug product. The specified impurities were qualified by the general repeat-dose or dedicated qualification studies in rats.

The risk for the environment resulting from the medicinal use of tirzepatide is considered negligible since it is a peptide and there is no relevant exposure of the environment.

5.4 Nonclinical Conclusions

Overall, the submitted nonclinical documentation is considered adequate to support the approval of Mounjaro (tirzepatide) in the proposed indication. The safety-relevant nonclinical data are included in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Biopharmaceutical Development

Throughout the clinical programme, two formulations of tirzepatide, a lyophilised formulation and a solution formulation, have been developed and used. The initial lyophilised formulation was administered by a syringe, whereas the solution formulation was either administered by a prefilled syringe (PFS) or single-dose pen (SDP). The final to-be-marketed drug product is a clear, colourless to slightly yellow, sterile solution for subcutaneous (SC) administration. It will be supplied as 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL and 15 mg/0.5 mL solution in an SDP.

The drug product that was used in all Phase 3 studies, i.e. the solution formulation, was intended for commercialisation.

Three biopharmaceutical studies were conducted to investigate the effect of formulation, drug delivery device and injection site on bioavailability.

Bioequivalence of single 5 mg SC doses of the lyophilised and solution formulations was demonstrated in healthy subjects. In the context of a population PK analysis, it was shown that the absorption rate constant (ka) of the lyophilised formulation was moderately lower, which was consistent with the observed 9% decreased C_{max}.

Following the administration of single 5 mg SC doses of tirzepatide by using a PFS or an SDP, bioequivalence was shown in healthy subjects.

Injection site, i.e. abdomen, upper arm and thigh, did not have an impact on the tirzepatide exposures following the administration of single 5 mg SC doses. Consequently, tirzepatide can be injected subcutaneously in the abdomen, thigh or upper arm.

ADME

The pharmacokinetic (PK) and pharmacodynamic (PD) properties of tirzepatide in healthy subjects and in patients with type 2 diabetes mellitus (T2DM) following single (0.25 mg to 8 mg) and multiple doses (0.5 mg to 15 mg) were evaluated in 10 Phase 1 studies. Pharmacokinetic data collected in two Phase 2 and seven Phase 3 studies were used exclusively for population PK as well as PK/PD analyses.

Absorption

Following single and multiple once weekly (QW) doses of tirzepatide, the peak plasma concentrations were reached after a median time of approximately 24 h. Based on the $AUC_{(0-\infty)}$ ratio following the SC and IV administration of tirzepatide, the absolute bioavailability was determined as approximately 80%.

Steady state exposures were reached after approximately four QW doses. Tirzepatide showed moderate accumulation, based on population PK *post hoc* parameters having an accumulation ratio of 1.7.

Overall, tirzepatide exposures increased with the dose. Whereas a trend of a less than dose-proportional increase was observed following a single dose, slightly more than dose-proportional increases were observed following multiple doses. Based on the population PK analysis, it can be assumed that tirzepatide exhibits linear PK across the investigated dose range. In view of the observed half-life following a single dose of tirzepatide and the accumulation ratio, time-independent PK is likely.

Based on the population PK *post hoc* parameters, higher exposures were observed in healthy subjects, presumably reflecting the higher baseline body weight of T2DM patients. Consequently, disease status was not identified as a significant covariate in the population PK analysis.

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Based on simulations with the population PK model, it is recommended that a dose should be administered as soon as possible within four days in case of a missed dose. If more than four days have passed, the missed dose should be skipped.

Distribution

Based on *in vitro* findings, tirzepatide was highly bound in human plasma with a mean percent bound of 99.06%. The B/P ratio of 0.5 suggests that tirzepatide is confined to the plasma compartment.

Based on population PK *post hoc* parameters, the apparent volume of distribution (Vd/F) at steady state in patients with T2DM was estimated at 10.3 L.

Metabolism and Elimination

Tirzepatide was primarily metabolised via proteolytic cleavages of the peptide backbone, β-oxidation of the C20 fatty diacid moiety and amide hydrolysis.

Tirzepatide was excreted via urine and faeces accounting for 50% and 20%, respectively, of the total radioactivity, suggesting that renal excretion was the primary route of elimination. The predominant circulating entity in plasma was unchanged tirzepatide (80%), and four minor metabolites were identified in plasma, each accounting for less than 5.7% of the total circulating radioactivity. No parent drug was detected in urine or faeces.

Based on population PK *post hoc* parameters, the apparent clearance (CL/F) in patients with T2DM following multiple tirzepatide doses was estimated at 0.0606 L/hr, resulting in a mean terminal half-life of 5.4 days.

Special Populations / Intrinsic Factors

The impact of liver function on the PK of tirzepatide following a single dose of 5 mg tirzepatide was investigated in a dedicated study in subjects with normal hepatic function and in subjects with mild to severe hepatic impairment. Overall, the tirzepatide exposures as well as t_{max} and $t_{1/2}$ were comparable across the control and hepatic impairment groups.

The impact of renal function on the pharmacokinetics of tirzepatide following a single dose of 5 mg tirzepatide was investigated in a dedicated study in subjects with normal renal function and in subjects with mild to severe renal impairment or end-stage renal disease (ESRD). The exposures increased only slightly in subjects with renal impairment. Whereas the half-life was comparable, t_{max} was shorter for the severe renal impairment cohort. Overall, these effects were deemed not to be clinically significant.

Using data from 19 Phase 1, Phase 2 and Phase 3 studies including sample records from 5802 subjects, a population PK analysis was conducted to identify factors that account for variability of the tirzepatide PK. The PK of tirzepatide was well described by a 2-compartment model with first-order absorption, linear elimination and interindividual variability (IIV) on absorption rate (ka), clearance (CL), central volume of distribution (Vc) and proportional residual error. The final model included the following covariates: study effect on bioavailability, body weight on clearance, body weight and fraction fat mass on volume of distribution, and lyophilised formulation on absorption rate. Overall, no dose adjustments are required based on any of the investigated covariates including gender, age, body weight and race.

Interactions

Tirzepatide, a 4.8 kDa peptide, is primarily subjected to proteolytic degradation and is not considered to be a substrate for cytochrome P450 (CYP) enzymes and drug transporters. Overall, there is a low clinical DDI risk involving human CYPs and membrane hepatic or renal transporters based on the *in vitro* risk assessment.

However, GLP-1 agonists have the potential to interact with co-administered compounds by delaying gastric emptying (GE). The impact of different doses of tirzepatide on GE was investigated in healthy

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subjects and patients with T2DM using acetaminophen as a marker molecule. At doses ≥ 5 mg, an impact on GE was observed, i.e. a delay in t_{max} and a decrease in C_{max} of acetaminophen. When tirzepatide was administered QW at 5 mg for 4 weeks, delay in GE was greatest following the administration of the first dose as shown by t_{max} prolonged by 1 h. After the fourth dose, the effect on GE was less evident. When applying a 5 mg/5 mg/10 mg/15 mg dose escalation regimen, the GE after the first 5 mg dose and the fourth 15 mg dose was comparable. Overall, these findings suggest that the impact on GE was greatest after the first dose and was less evident after multiple doses.

The potential effect of tirzepatide on drugs commonly used by subjects with T2DM and with different solubility and permeability properties and/or narrow therapeutic indices, including acetaminophen, atorvastatin, digoxin, ethinylestradiol, lisinopril, metformin, metoprolol, norgestimate, sitagliptin and S-warfarin was investigated. The selection of victim drugs was in line with previously approved GLP-1 receptor agonists.

The effect of a single 5 mg dose on combination oral contraceptive (OC) PK at steady state was investigated in healthy female subjects. Whereas C_{max} of ethinylestradiol and norgestimate was significantly decreased by 55% and 66%, respectively, the impact on $AUC_{0\text{-tlast}}$ was less pronounced, i.e. 16% and 20%. Delays in t_{max} of 2.5 h to 4.5 h were observed. However, the decrease of AUC was more pronounced as compared to drug-drug interaction (DDI) studies with other GLP-1 receptor agonists.

Instead of clinical DDI studies, a PBPK modelling approach was used to assess the impact of tirzepatide on the exposures of the aforementioned drugs. Since only limited clinical data on tirzepatide DDIs were available, the PBPK models developed for the co-administered drugs were verified using primarily observed data from clinical DDI studies with dulaglutide. Overall, the verifications suggest adequate performance of the PBPK models. Based on the analysis and also in view of the current knowledge on the DDI potential of other GLP-1 receptor agonists, no dose adjustments are required for the tested drugs when concomitantly administered with tirzepatide.

Mechanism of Action and primary Pharmacology

Tirzepatide is synthetic peptide with dual-agonist activity at both the human glucose-dependent insulinotropic polypeptide (GIP) and human glucagon-like peptide-1 (GLP-1) receptors. A fatty-diacid portion was attached at position 20 to optimise the uptake and metabolism. This arrangement enables albumin binding, which eventually leads to a longer half-life allowing a QW dosing regimen.

The PD properties of tirzepatide, including the effects on blood glucose and body weight, were investigated in healthy subjects and in patients with T2DM. In summary, the administration of 15 mg QW tirzepatide with dose escalation improved blood glucose regulation by increasing insulin sensitivity and insulin secretion, as well as by reducing glucose-stimulated glucagon concentrations as compared with placebo and 1 mg QW semaglutide. Furthermore, greater HbA1c-lowering efficacy was observed for tirzepatide as compared with placebo and semaglutide. The administration of tirzepatide resulted in reduced food intake in the *ad libitum* meal test, contributing to the observed weight loss.

Secondary Pharmacology (Safety)

No tQT study was conducted. A concentration effect analysis for QTcF and PR interval based on data from Phase 1 and Phase 2 studies suggested the absence of an unacceptable prolongation in cardiac repolarisation or any impact on PR interval compared to placebo across the therapeutic dose range of tirzepatide.

As part of the exposure-response analysis, the relationships of QTcF and PR intervals matched by date to the observed tirzepatide concentration at Week 40 and Week 52 in the Phase 3 studies were assessed. Overall, the QTcF and PR intervals were within clinically acceptable limits.

Of note, transient increases in heart rate were observed following tirzepatide treatment, particularly during the early dose-escalation period, using linear regression analysis. No data at supratherapeutic exposure are available.

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Pharmacodynamic Interactions with other medicinal Products or Substances

The impact of tirzepatide on GE was studied using acetaminophen as a gastric emptying marker (see above).

Relationship between Plasma Concentration and Effect

The relationship between tirzepatide exposure and efficacy (fasting glucose (FG), glycosylated haemoglobin A1c (HbA1c) and body weight) and safety endpoints (nausea, vomiting and diarrhoea) in patients with T2DM was investigated in an exposure-response analysis using data from seven Phase 3 studies.

The time course of HbA1c was described by an indirect response model dependent on FG. A statistically significant relationship between body weight change over time and the tirzepatide concentration led to a reduced EC_{50} on FG, suggesting that body weight loss was associated with an improved effect of tirzepatide. The model predicted significant glycaemic improvements following the administration of 5 mg, 10 mg or 15 mg QW tirzepatide doses reasonably well. The largest effect was achieved with the 5 mg dose. A plateau was approached when the higher doses were administered.

The relationship between tirzepatide exposure and body weight was best described by a linear drug effect model. Sex and Japanese race were identified as significant covariates and were included in the final model. The model predicted a clear dose-response relationship, and no plateau was observed across the administered doses.

A discrete-time Markov model was used to estimate transition probabilities between nausea, vomiting and diarrhoea adverse event (AE) states (no, mild or moderate/severe event) and to investigate the impact of tirzepatide effects and covariates on these probabilities. Sex, Japanese and Hispanic ethnicities were identified as significant covariates. Overall, the dose escalation regimen seems to have mitigated the incidence of GI AEs, since the incidence rate was substantially decreased once steady state concentrations for the three proposed maintenance doses of 5 mg, 10 mg and 15 mg were reached.

Immunogenicity

Across the Phase 3 studies, 51.1% of patients treated with tirzepatide developed treatment-emergent antidrug antibodies (TE ADAs), and the proportions were comparable across the three tirzepatide dose groups. Only 1.9% and 2.1% showed neutralising activity on the GIP receptor and GLP-1 receptor. In the context of the population PK analysis, no statistically significant relationship between ADA and clearance was identified.

6.2 Dose Finding and Dose Recommendation

Two multicentre, randomised, double-blind Phase 2 trials found the dose recommendations. The 26-week study GPGB examined four doses of Mounjaro (1, 5, 10 and 15 mg QW) vs. dulaglutide 1.5 mg QW and placebo. The 12-week study GPGF examined various dose escalation schemes over a range from 2.5 mg to 15 mg. Both studies used the change in HbA_{1c} (ΔA1C) from baseline as the primary efficacy endpoint. In GPGB, tirzepatide was superior to placebo for all the four doses tested, while superiority to dulaglutide 1.5 mg was achieved with doses ≥ 5 mg.

Tirzepatide dose	LSM differences [95% CI] in ΔA1C (%) at Week 26		
	Placebo	Dulaglutide	
1 mg	-1.00 [-1.22, -0.79]	0.15 [-0.08, 0.38]	
5 mg	-1.67 [-1.88, -1.46]	-0.52 [-0.72, -0.31]	
10 mg	-1.83 [-2.04, -1.61]	-0.67 [-0.89, -0.46]	**Source: Table GPGB 11.2.**
15 mg	-1.89 [-2.11, -1.67]	-0.73 [-0.95, -0.52]	

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Tirzepatide 15 mg was associated with the highest rate of gastrointestinal (GI) adverse events.

GPGF confirmed the robust glucose-lowering efficacy observed in GPGB, and showed that stepwise dose titration can ameliorate the prevailing GI AEs. It was decided to continue with doses of 5, 10 and 15 mg QW in the Phase 3 studies.

6.3 Efficacy

The SURPASS development programme for tirzepatide included seven Phase 3 studies sharing key design features. The table below summarises the global Phase 3 studies SURPASS 1 to 5, which only differed in the duration of the main treatment period, the comparator, the prior antidiabetic treatment reflecting different stages of T2DM, and open-label versus double-blind design. Two additional trials were local studies in Japan.

The evidence supporting glucose-lowering efficacy of tirzepatide is overwhelming. Its effect on HbA_{1c} was superior not only to placebo, but also to the active comparators, including the GLP-1 receptor-agonist semaglutide and basal insulins. Moreover, tirzepatide was still effective in patients failing glycaemic control on prior treatment with basal insulin (SURPASS-5).

Pivotal Phase 3 trials of the «SURPASS» development programme

Study	Duration [weeks]	Comparator	Antihyperglycaemic background medication	Tirzepatide dose (mg)	LS mean difference change in HbA_{1c} [95% CI] §
SURPASS-1	40	Placebo (n=113)	None §§	5 (n=121) 10 (n=121) 15 (n=120)	-1.66 [-1.96, -1.36] -1.62 [-1.92, -1.32] -1.60 [-1.91, -1.30]
SURPASS-2	40	Semaglutide (n=468)	Metformin	5 (n=470) 10 (n=469) 15 (n=469)	-0.15 [-0.28, -0.03] -0.39 [-0.51, -0.26] -0.45 [-0.57, -0.32]
SURPASS-3	52	Insulin Degludec (n=359)	Metformin ± SGLT2i	5 (n=358) 10 (n=360) 15 (n=358)	-0.60 [-0.74, -0.45] -0.76 [-0.90, -0.61] -0.89 [-1.03, -0.74]
SURPASS-4	104	Insulin Glargine (n=998)	Metformin ± SU ± SGLT2i	5 (n=328) 10 (n=326) 15 (n=337)	-0.72 [-0.86, -0.58] -0.91 [-1.05, -0.77] -1.02 [-1.15, -0.89]
SURPASS-5	40	Placebo (n=119)	Insulin glargine ± Metformin	5 (n=116) 10 (n=118) 15 (n=118)	-1.24 [-1.48, -1.01] -1.53 [-1.77, -1.30] -1.47 [-1.71, -1.23]

§ Treatment-regimen estimand
§§ Treatment-naïve for injectable therapies and no use of OAMs for ≥ 3 months.
SGLT2i = SGLT2 inhibitor SU = sulphonylurea

Likewise, tirzepatide reduced fasting plasma glucose and body weight (not shown).

The SURPASS-3 CGM substudy showed that tirzepatide-treated patients spend significantly more time in the target range (71 - 140 mg/dL) than patients in the insulin degludec group (treatment difference [95% CI]: 24.55% [15.77, 33.34]). Likewise, the SURPASS-3 MRI substudy showed that liver fat content at Week 52 was significantly lower in tirzepatide-treated patients (8.2% to 10.1%) as compared with those in the insulin degludec group (13.2%).

6.4 Safety

Tirzepatide is a novel dual agonist based on the sequence of GLP-1 and GIP. Hence, the safety profile of the new drug is expected to principally match with that of GLP-1 receptor-agonists (GLP-1RA). Additional aspects specifically related to GIP receptor activation remain to be established.

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The safety evaluation was based on the following set of clinical studies (19 in total): 10 biopharmaceutical and clinical pharmacology studies, 2 Phase 2 clinical studies, 5 global Phase 3 studies and 2 regional Phase 3 studies conducted in Japan.

The treatment duration of these trials ranged from 12 to 26 weeks in the Phase 2 studies, and from 40 to 104 weeks in the Phase 3 studies (all with a 4-week safety follow-up). The overall exposure in this comprehensive study programme was substantial. A total of 7769 patients received study drug in the nine completed Phase 2/3 studies. Of these, 5415 patients received tirzepatide in the Phase 2 and 3 studies for 4833.1 patient-years. A total of 2375 patients received tirzepatide for ≥ 52 weeks in the Phase 2/3 studies, with 535 receiving treatment for ≥78 weeks.

Assessment of the **CV safety** was based on the CV Meta-Analysis Set (AS5) comprising all placebo- or active-controlled Phase 2/3 studies with a treatment period lasting ≥ 26 weeks. This CV meta-analysis included patients with a broad spectrum with regard to the T2DM disease stages, background antidiabetic medications and renal impairment. Primary endpoint was a 4-point MACE (CV death, myocardial infarction, stroke, hospitalisation for unstable angina).

Baseline demographics and CV risk characteristics in the integrated analysis population were comparable between the pooled tirzepatide group and the pooled comparator group.

The final analysis performed after accrual of 142 primary endpoint events (adjudicated 4-point MACE) support the CV safety of tirzepatide. In line with previous findings for several GLP-1 analogues, and suggesting even a CV benefit, the HR [95% CI] for the primary endpoint was 0.80 [0.57, 1.11]. Moreover, study GPGM was a large, long-term study specifically in patients with increased CV risk. This study contributed the majority of events (109 4-point MACE) for the CV safety meta-analysis, and the within-study HR [95% CI] was 0.74 [0.51, 1.08].

In conclusion, the findings from this meta-analysis support the CV safety of tirzepatide. Additional data on CV safety will be provided from the currently ongoing CVOT (Study I8F-MC-GPGN) using dulaglutide as an active comparator.

As expected from the safety profile of GLP-1RAs, **gastrointestinal adverse events** were the most common TEAEs reported with tirzepatide. These TEAEs were mostly mild or moderate in severity, resulting in dose-dependent permanent treatment discontinuation rates from 3% to 7%.

	n (%)					TZP_ALL vs. Placebo p-value[a]
Preferred term	TZP 5 mg (N=237)	TZP 10 mg (N=240)	TZP 15 mg (N=241)	TZP_ALL (N=718)	Placebo (N=235)	
Nausea	29 (12.2)	37 (15.4)	44 (18.3)	110 (15.3)	10 (4.3)	<0.001
Diarrhoea	28 (11.8)	32 (13.3)	39 (16.2)	99 (13.8)	21 (8.9)	0.050
Nasopharyngitis	25 (10.5)	16 (6.7)	23 (9.5)	64 (8.9)	33 (14.0)	0.027
Decreased appetite	13 (5.5)	23 (9.6)	27 (11.2)	63 (8.8)	3 (1.3)	<0.001
Dyspepsia	19 (8.0)	18 (7.5)	13 (5.4)	50 (7.0)	6 (2.6)	0.013
Vomiting	12 (5.1)	12 (5.0)	22 (9.1)	46 (6.4)	5 (2.1)	0.010
Constipation	14 (5.9)	14 (5.8)	16 (6.6)	44 (6.1)	3 (1.3)	0.003
Lipase increased	7 (3.0)	3 (1.3)	13 (5.4)	23 (3.2)	6 (2.6)	0.602
Hyperglycemia	6 (2.5)	5 (2.1)	4 (1.7)	15 (2.1)	47 (20.0)	<0.001

§ This figure has been taken from «Summary of Clinical Safety» (Module 2.7.4.)

As illustrated for the composite of nausea/vomiting/diarrhoea, the incidence of GI AEs was highest during the dose-escalation period of tirzepatide and saturated after reaching the maintenance dose at Week 24.

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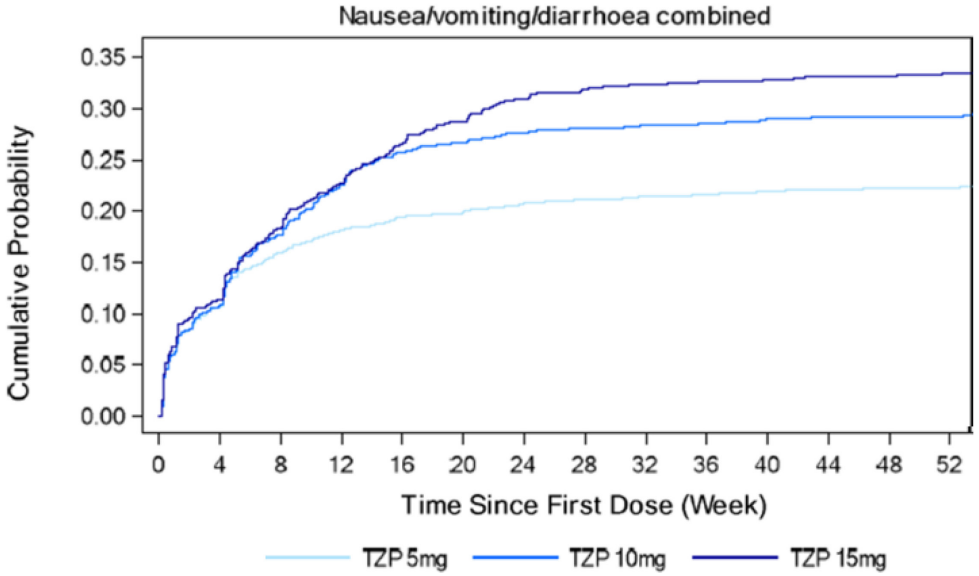

Figure 2.7.4.5 §
Plot of the time to onset of nausea, vomiting, diarrhoea
Phase 3 dose-effect analysis (AS2)

§ This figure has been taken from «Summary of Clinical Safety» (Module 2.7.4.)

In the head-to-head comparison of the Phase 3 study GPGL, GI AEs occurred at similar incidences in tirzepatide-treated patients and patients treated with the GLP-1RA semaglutide 1 mg. Nevertheless, the rate of permanent study drug discontinuation due to GI AEs was slightly higher with tirzepatide 10 mg and 15 mg (each 4.3%) than with semaglutide 1 mg (3.2%). This imbalance was even more pronounced in a Japanese population with dulaglutide 0.75 mg as comparator (0.6% vs. 6.9% [tirzepatide 15 mg]). The modified dose-escalation scheme in the Phase 3 studies improved the GI tolerability compared with that observed in the Phase 2 study GPGB.

Severe GI events may lead to dehydration, but no imbalance was observed in the placebo-controlled studies.

Overall, 64 events of suspected **pancreatitis** occurred in 61 (1.13%) tirzepatide-treated patients. Fourteen events of acute pancreatitis (all of mild to moderate severity) in 13 (0.24%) tirzepatide-treated patients were adjudication-confirmed (no cases adjudicated as chronic pancreatitis or unknown). The prevalence of adjudication-confirmed acute pancreatitis across three tirzepatide dose groups was comparable. The exposure-adjusted incidence rate (patients/100 patient-years) for treatment-emergent adjudication-confirmed pancreatitis was 0.23 patients per 100 patient-years for TZP_ALL and 0.14 patients per 100 patient-years for pooled comparators. Tirzepatide was associated with increases in p-amylase and lipase. These elevations in pancreatic enzymes were consistent with those observed for GLP-1 receptor agonist comparators, but were numerically larger in the tirzepatide 15 mg group.

No cases of **MTC or C-cell hyperplasia** were identified across all Phase 2/3 studies. Tirzepatide treatment also induced no marked increases in calcitonin.

Treatment with tirzepatide in patients with T2DM was not associated with an unacceptable risk of **hypoglycaemia**. Tirzepatide-induced severe hypoglycaemia was a rare event. The risk of hypoglycaemia with tirzepatide was comparable with, and partially slightly exceeding, that observed with currently approved GLP-1RAs. From a general perspective, the incidence of hypoglycaemic events (no matter what category) was lower in tirzepatide-treated patients than in patients receiving a basal insulin.

No **anaphylactic reactions** were observed. The percentage of patients reporting potential immediate hypersensitivity reactions was similar in tirzepatide- and placebo-treated patients (0.6% vs. 0.4%).
While it was generally low, the percentage of patients reporting potential non-immediate hypersensitivity reactions was increased in tirzepatide-treated patients (2.6%) compared to placebo (1.3%). This imbalance was primarily driven by allergic rhinitis.
Most potential hypersensitivity reactions were mild or moderate. Only four (0.08%) tirzepatide-treated patients in the Phase 3 studies reported serious or severe events.

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In conclusion, there is no critical safety concern of hypersensitivity reactions related to tirzepatide.

A higher percentage of tirzepatide-treated patients reported «**injection site reactions**» (3.2% versus 0.4% in the placebo group). Moreover, the percentage reporting treatment-emergent «injection site reactions» correlated with the tirzepatide dose (TZP 5 mg, 1.94%; TZP 10 mg, 2.70%; TZP 15 mg, 3.50%). None of the «injection site reactions» identified were severe or serious.

The majority of injection site reactions occurred > 6 hours to 14 days after tirzepatide injection. Most common symptoms were erythema and pruritus. The number of patients reporting multiple events increased with a higher tirzepatide dose.

Collectively, the findings support an association of tirzepatide treatment with «injection site reactions». Frequency and severity appear tolerable.

The **immunogenicity** of tirzepatide was prominent: there was a marked increase in the percentage of TE ADA+ patients in the tirzepatide groups compared with placebo. The percentage of TE ADA+ patients was similar across the three tirzepatide dose groups. Hypersensitivity reactions occurred with similar frequencies in TE ADA+ and TE ADA- patients. Injection site reactions were more frequent in TE ADA+ patients than TE ADA- patients. All of these events were non-serious and non-severe.

Across the Phase 3 trials, 18 (0.35%) tirzepatide-treated patients showed worsening of fundoscopic findings. The incidence in the individual trials ranged from 0% (GPGK) to 1.13% (GPGP), with no meaningful excess for “tirzepatide versus comparator”. None of the 18 patients had a SAE from the SOC of «eye disorders».

A customised MedDRA search in the placebo-controlled analysis set yielded no «potential **diabetic retinopathy**» event in tirzepatide-treated patients versus two (0.9%) events in the placebo controls.

The same search in the dose-effect analysis set detected 37 (0.7%) tirzepatide-treated patients with a potential diabetic retinopathy complication. There was no dose-dependency. Four of the 37 «potential diabetic retinopathy complication» events were categorised as serious or severe TEAEs. An ongoing dedicated addendum study to SURPASS-CVOT will further investigate this potential safety issue.

The overall incidences of **malignancies** through all Phase 2/3 studies (comprising 5415 tirzepatide-treated patients) were similar for patients in the tirzepatide group (1.02%) and patients in the comparator groups including semaglutide (0.64), insulin degludec (0.28%), insulin glargine (1.90%), dulaglutide (1.88%) and placebo (1.60%). The numbers of events reported for any type of malignancy were rather small. Only basal cell carcinoma (five events [0.09%]), squamous cell carcinoma (three events [0.06]) and adenocarcinoma of the colon (three events [0.06%]), renal cell carcinoma (three events [0.06%]), renal neoplasm (three events [0.06%]) and prostate cancer (three events [0.10%]) were more common in the tirzepatide-treated patients. Then again, these rates were not increased above those seen in comparator arms reporting the same type of events.

There were two cases of pancreatic cancer in tirzepatide-treated patients (see corresponding Section for details on pancreatotoxicity).

The applicant has committed to the continued careful assessment of malignancies in ongoing studies and postmarketing pharmacovigilance.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Medical and regulatory context

T2DM is a progressive disease typically requiring stepwise intensification of pharmacotherapy. There is a need for novel medications offering a robust and sustained glucose-lowering efficacy at different stages of the disease, preferably combining benefits related to CV risk, kidney function or body weight control. In addition, slowing down or reversing progressive insulin resistance is desirable.

Tirzepatide is a novel dual agonist potentially combining the favourable effects of GLP-1 receptor-agonists and GIP activation.

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Beneficial effects and uncertainties

The clinical pharmacology package was extensive and covered all the relevant aspects. Overall, the pharmacokinetic and pharmacodynamic properties of tirzepatide are in line with those of previously approved GLP-1 receptor agonists. No dose adjustments are recommended for patients with mild to severe hepatic impairment or for patients with mild to severe renal impairment as well as ESRD. A population pharmacokinetic analysis revealed that no dose adjustments are necessary based on body weight, age, sex or race. The DDI risk can be considered low. No unacceptable prolongation in cardiac repolarisation or any impact on PR interval compared to placebo was observed across the therapeutic dose range of tirzepatide.

As summarised below, tirzepatide (TZP) treatment caused marked reductions in HbA_{1c} and body weight. This finding was consistent across patient populations with different disease-related baseline characteristics including duration of T2DM (mean ~4.7 to ~13.3 years), background antihyperglycaemic treatment and the CV risk.

Study	Comparator	TZP dose	LS mean treatment difference [95% CI] (treatment-regimen estimand)	
			HbA_{1c} (%)	Body Weight (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 (IDeg)	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 Glargine (IGlar)	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]
SURPASS J-mono	Dulaglutide	5 mg 10 mg 15 mg	-1.09 [-1.27, -0.90] -1.27 [-1.45, -1.08] -1.53 [-1.71, -1.35]	-5.2 [-6.4, - 4.1] -7.9 [-9.1, -6.8] -10.1 [-11.3, -9.0]

Both the glucose-lowering and weight-reducing effects were compelling.Thus, tirzepatide's glucose-lowering effect was superior to that of active comparators such as GLP-1RAs (semaglutide and dulaglutide) and basal insulins (IDeg and IGlar).

The treatment effect on HbA_{1c} and body weight was consistent across major subgroups. The clinical relevance of potential differences in efficacy for specific subgroups (age, BMI, race) observed across the Phase 3 trials remains uncertain.

Results for other secondary endpoints further substantiated the efficacy of tirzepatide. Also remarkable are the outstanding responder rates (proportion of patients reaching glycaemic target HbA_{1c}<7%) of about 80% and above. In addition, considerable proportions of tirzepatide-treated patients (~40% in the 15 mg group across all studies) achieve normal levels of glycaemia (HbA_{1c}<5.7%). Furthermore, the results of a CGM substudy showed that tirzepatide-treated patients spent significantly more time in the target range (70 - 140 mg/dL) than patients treated with IDeg (estimated treatment difference [95% CI]: 24.55% [15.77%, 33.34%]).

Finally, exploratory results suggested beneficial effects of tirzepatide on beta-cell function, lipid parameters, liver fat content and patient-reported outcomes.

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Unfavourable effects and uncertainties

Although the impact on AUC was less pronounced than on C_{max} when OCs were co-administered with tirzepatide, the decrease of AUC was more pronounced as compared to other GLP-1 receptor agonists

The safety profile of the dual-agonist tirzepatide established in an extensive clinical programme resembled that described for GLP-1RAs. More specifically, tirzepatide's safety profile was dominated by gastrointestinal (GI) adverse events, mainly nausea, vomiting and diarrhoea. Their severity was mostly mild to moderate, their incidence highest immediately after initiation, saturating more or less towards the end of the dose-escalation period. The modified dose-escalation scheme used in the Phase 3 studies improved the GI tolerability compared with that observed in the Phase 2 study GPGB.

Other potential safety concerns relate to hypoglycaemia, pancreatic function, renal safety, diabetic retinopathy, thyroid cancer, immunogenicity, injection site reactions and hypersensitivity.

Tirzepatide-treatment of T2DM is associated with an acceptable risk of hypoglycaemia comparable with, and partially slightly exceeding, that of marketed GLP-1RAs. Severe hypoglycaemia was rare.

Exposure-adjusted incidence rates for adjudication-confirmed treatment-emergent pancreatitis in tirzepatide-treated patients was low, but increased compared with pooled comparators (0.23 versus 0.14 patients per 100 patient-years). Tirzepatide was associated with increases in p-amylase and lipase that were most prominent in the tirzepatide 15 mg group and similar to those observed for GLP-1RA comparators.

Tirzepatide-treated patients reported treatment-emergent renal events at an incidence of 1.27% without dose-dependency. There was no critical imbalance from any of the comparators including placebo. Compared with placebo, tirzepatide-treatment was associated with a slight numerical excess in the drop of eGFR decline which was not dose-dependent. At the same time, all doses of tirzepatide improved UACR, while UACR worsened in placebo control. The clinical relevance of the latter finding remains uncertain.

There was no clear association of tirzepatide treatment with diabetic retinopathy progression in the tirzepatide arm. An ongoing dedicated addendum study to SURPASS-CVOT will further investigate this issue.

The safety data from the Phase 2/3 studies provided no evidence of an increased risk of medullary thyroid cancer (MTC) or C-cell hyperplasia with tirzepatide treatment, which has been observed in rats exposed to the drug. The Phase 2/3 programmes did not examine patients with MTC or multiple endocrine neoplasia syndrome type 2 (MEN 2).

Tirzepatide-treatment was associated with marked immunogenicity (~50% TE ADA+ post-baseline). Repercussions on hypersensitivity reactions were negligible (similar frequency in TE ADA+ and TE ADA- patients).On the other hand, injection site reactions were more frequent in TE ADA+ patients than TE ADA- patients, but all injection site reactions were non-serious and non-severe.

No safety data related to bone function and muscle disorders (e.g. CK increase) have been described. However, a meta-analysis of GLP-1RAs and preclinical data for tirzepatide suggested no harmful effects on bone function.

The placebo-controlled Phase 2/3 studies revealed a minor imbalance for adverse events of acute gall bladder disease. The clinical relevance is uncertain, but patients with acute gall bladder disease should be monitored adequately.

In conclusion, the safety profile of tirzepatide is dominated by AEs typical for GLP-1RAs. No additional critical or prohibitive safety signal has been detected. At the same time, tirzepatide's efficacy is superior to that of the GLP-1RAs semaglutide and dulaglutide and standard basal insulins.

Benefit-risk balance

The benefit-risk ratio is considered positive. Minor uncertainties regarding potential rare adverse events related to the GIP agonism remain.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to 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 reference document, which is valid and relevant 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. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼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® Pre-filled pen

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.

Indications/Uses

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.

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.

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 with a narrow therapeutic window are administered simultaneously with tirzepatide as an increased release due to prolonged gastric retention time may slightly increase exposure to the medicinal product.

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 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.

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.

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

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.

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).

Gastrointestinal disorders
Very common: Nausea (18 %), diarrhoea (15 %)
Common: abdominal pain, vomiting, dyspepsia, constipation, meteorism, eructation, flatulence, gastroesophageal reflux disease

Metabolism and nutrition disorders
Very common:
Hypoglycaemia* when used with sulfonylurea or insulin:

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

Common:
Hypoglycaemia* when used with metformin and SGLT2i, decreased appetite
Uncommon:
Hypoglycaemia* when used with metformin

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

General disorders and administration site conditions
Common: Fatigue, injection site reactions.

Description of selected adverse reactions and additional information

Hypoglycemia

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

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 and safety associated with the development of ADA.

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

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

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 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 improves insulin sensitivity.

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

Tirzepatide decreases food intake.

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 type 2 diabetes, 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.

Pancreatic enzymes

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

Cardiac electrophysiology (QTc intervals)

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

Clinical efficacy

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.

Cardiovascular Evaluation

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).

Blood Pressure

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.

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 patients receiving placebo.

Special populations

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

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.

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

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.

Authorization number

68726 (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)

Marketing authorization holder

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

Date of revision of the text

October 2022