Taiwan Food and Drug Administration

Assessment Report

Trade Name：
猛健樂注射劑 2.5 毫克/0.5 毫升/ MOUNJARO Injection 2.5mg/0.5mL
猛健樂注射劑 5 毫克/0.5 毫升/ MOUNJARO Injection 5 mg/0.5mL
猛健樂注射劑 7.5 毫克/0.5 毫升/ MOUNJARO Injection 7.5mg/0.5mL
猛健樂注射劑 10 毫克/0.5 毫升/ MOUNJARO Injection 10mg/0.5mL
猛健樂注射劑 12.5 毫克/0.5 毫升/ MOUNJARO Injection 12.5mg/0.5mL
猛健樂注射劑 15 毫克/0.5 毫升/ MOUNJARO Injection 15mg/0.5mL

Active Ingredient：Tirzepatide

License Number：MOHW-PI 028463、MOHW-PI 028464、MOHW-PI 028465、MOHW-PI 028466、MOHW-PI 028467、MOHW-PI 028468

Applicant：台灣禮來股份有限公司

Approval Date：2023/4/20

Indication：
作為飲食及運動療法之外的輔助治療，用於改善第二型糖尿病成人病人之血糖控制。
說明: Mounjaro 可做為單一療法或與其他糖尿病治療藥物合併使用。
使用限制:

- **MOUNJARO 尚未在有胰臟炎病史的病人中進行研究。**
- **MOUNJARO 不可用於第一型糖尿病病人。**

As an adjunct to diet and exercise to improve glycemic control in adults

with type 2 diabetes mellitus

- **as monotherapy or in addition to other medicinal products for the treatment of diabetes.**

Limitations of Use

- **MOUNJARO has not been studied in patients with a history of pancreatitis**
- **MOUNJARO is not indicated for use in patients with type 1 diabetes mellitus.**

Background Information

Trade Name	猛健樂注射劑 2.5 毫克/0.5 毫升/ MOUNJARO Injection 2.5mg/0.5mL 猛健樂注射劑 5 毫克/0.5 毫升/ MOUNJARO Injection 5 mg/0.5mL 猛健樂注射劑 7.5 毫克/0.5 毫升/ MOUNJARO Injection 7.5mg/0.5mL 猛健樂注射劑 10 毫克/0.5 毫升/ MOUNJARO Injection 10mg/0.5mL 猛健樂注射劑 12.5 毫克/0.5 毫升/ MOUNJARO Injection 12.5mg/0.5mL 猛健樂注射劑 15 毫克/0.5 毫升/ MOUNJARO Injection 15mg/0.5mL
Active Ingredient(s)	Tirzepatide
Applicant	台灣禮來股份有限公司
Dosage Form & Strengths	注射劑, 2.5mg/0.5 mL, 5mg/0.5 mL, 7.5mg/0.5mL, 10mg/0.5mL, 12.5mg/0.5mL, 15mg/0.5mL
Indication	作為飲食及運動療法之外的輔助治療，用於改善第二型糖尿病成人病人之血糖控制。 說明: Mounjaro 可做為單一療法或與其他糖尿病治療藥物合併使用。 使用限制: ● MOUNJARO 尚未在有胰臟炎病史的病人中進行研究 。 ● MOUNJARO 不可用於第一型糖尿病病人。 As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus • as monotherapy or in addition to other medicinal products for the treatment of diabetes. Limitations of Use • MOUNJARO has not been studied in patients with a history of pancreatitis

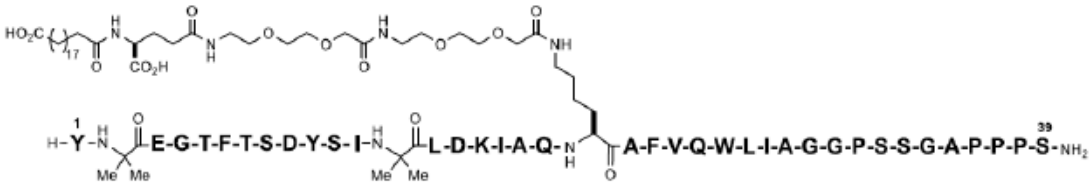
	• MOUNJARO is not indicated for use in patients with type 1 diabetes mellitus.
Posology	詳見仿單
Pharmacological Category **ATC Code**	A10BX16

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

Drug Substance

The drug substance, tirzepatide, is chemically designated as L-Serinamide, L-tyrosyl-2-methylalanyl-L-α-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-α-aspartyl-L-tyrosyl-L-seryl-L-isoleucyl-2-methylalanyl-L-leucyl-L-α-aspartyl-L-lysyl-L-isoleucyl-L-alanyl-L-glutaminyl-N^6-[(22S)-22,42-dicarboxy-1,10,19,24-tetraoxo-3,6,12,15-tetraoxa-9,18,23-triazadotetracont-1-yl]-L-lysyl-L-alanyl-L-phenylalanyl-L-valyl-L-glutaminyl-L-tryptophyl-L-leucyl-L-isoleucyl-L-alanylglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl and has the following structure:



It is a white to practically white solid. The molecular formula and the molecular weight are $C_{225}H_{348}N_{48}O_{68}$ and 4810.52 Da (monoisotopic mass) or 4813.45 Da (average mass IUPAC 2007), respectively.

Adequate information of characterization of the drug substance has been provided. The chemical structure of the drug substance was elucidated by a combination of LC-MS, LC-MS/MS of intact molecule, LC-MS peptide mapping, chiral GC-MS, RP-HPLC and IC, NMR, far-UV CD spectroscopy, FTIR spectroscopy, near-UV CD spectroscopy, composition gradient multiangle light scattering, and cell-based bioassays.

The drug substance specifications include tests for identification, assay, purity, related substances, high molecular weight species, residual solvents, description, water content, bacterial endotoxins, TAMC and TCYMC.

Drug Product

The drug product, Mounjaro Injection, is supplied in six strengths (2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL), which is a clear to

opalescent, colorless to slightly yellow or brown, essentially free of particles, sterile, and non-pyrogenic parenteral solution for subcutaneous administration. The excipients used in the drug product formulation comply with the compendial monographs.

The drug product specifications include identity, assay, purity, related substances, high molecular weight species, description, color, clarity, bacterial endotoxin, sterility, pH, osmolality, particle matter, volume of injection, and syringe functionality. The autoinjector specifications include identity, dose accuracy, visual/functional inspection, and injection time. Analytical methods are described well and validated.

Stability studies of the drug product under long term condition (5°C) and accelerated condition (30°C/65% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Pharmacology data demonstrated that tirzepatide potently and selectively activates the rat, mouse, monkey, and human GLP-1 and GIP receptors. The in vivo animal studies showed that tirzepatide improved glycemic control compared with GLP-1RAs by enhancing β-cell function and improving whole-body insulin sensitivity with weight-loss-dependent (GLP-1 and GIP receptor agonism) and weight-loss-independent (GIP receptor agonism) manner.

Safety pharmacology studies indicated that tirzepatide had no effects on the CNS and respiratory systems in the 1-month toxicity of monkeys. Consistent with the reported pharmacological effects of GLP-1 on the cardiovascular system, tirzepatide increased blood pressure and heart rate and decreased cardiac contractility in monkeys after a single subcutaneous injection.

2.2.2 Toxicological Studies

The pivotal repeated-dose toxicity studies included a 6-month study in rats and a 6-month study in monkeys. Most findings were generally consistent with, or secondary to, incretin pharmacology and included decreased body weight gain and/or body weight loss and decreased food consumption. No direct target organ toxicities were identified in either rats or monkeys. The NOAELs in repeated-dose toxicology studies were the highest doses administered and provided safety margins of approximately 1.35~1.96 fold based on AUC for the maximum recommended human dose of 15 mg/week.

Tirzepatide showed no evidence of genotoxicity in an in vivo micronucleus study. In the rat 2-year carcinogenicity study, neoplastic effects were limited to the thyroid C-cell, consistent with findings reported in the thyroid for the long-acting GLP-1 receptor agonist class. No

tirzepatide-related neoplastic findings occurred in RasH2 transgenic mice after 6 months of tirzepatide treatment.

Reproductive and developmental studies indicate that tirzepatide did not impact male fertility but adversely affected female fertility (decreased numbers of corpora lutea, decreased numbers of implantation sites and viable embryos, and disrupted estrous cycles). Development effects (reduced fetal weights in both species, reduced pup weights, and increased numbers of malformations and developmental variations in rats) occurred only in conjunction with maternal toxicity (body weight loss). Tirzepatide did not impact juvenile development.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following subcutaneous administration of tirzepatide, median t_{max} was achieved ~24 hours (range 8 to 72 hours) post-dose. The absolute bioavailability of a 5-mg subcutaneous dose of tirzepatide was 80%. Tirzepatide PK was generally similar between healthy participants and patients with T2DM. The exposure to tirzepatide increased proportionally with increasing dose levels in the 0.25- to 15-mg dose range. Accumulation after multiple dose administration was approximately 1.7-fold.

Mean apparent volume of distribution (Vd/F) in patients with T2DM after multiple dosing was 10.3 L. After 0.5-mg intravenous bolus administration, the mean volume of distribution (Vz) was 5.52 L. Tirzepatide was highly protein bound in human plasma with a mean percent bound of 99.06%. In the human ^{14}C-TZP study, ~50% of the administered radioactivity was excreted in the urine and ~21% was excreted in feces. Tirzepatide was eliminated through metabolism with no intact tirzepatide observed in urine or feces. The primary metabolic pathways of tirzepatide were proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety, and amide hydrolysis. Mean terminal half-life was ~5 days.

2.3.2 Interaction Studies

The clearance of tirzepatide is not mediated by cytochrome P450 enzymes or drug transporters. Concomitantly administered drugs are not expected to influence tirzepatide PK.

In Study GPGA, a delay was observed in acetaminophen t_{max} of approximately 1 hour and a maximum decrease in C_{max} of approximately 50% with no clinically relevant impact on AUC after the first 5-mg dose of tirzepatide, thereby suggesting delay in gastric emptying. The impact of tirzepatide on PK of combination OC was studied by administering a combination OC (ethinyl estradiol 0.035 mg and norgestimate 0.25 mg) with a single 5-mg dose of tirzepatide (Study GPGR). Mean C_{max} of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%, 66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%,

respectively. A delay in t_{max} of 2.5 to 4.5 hours was observed.

2.3.3 Special Populations

Based on population PK analysis, the mean effects of intrinsic factors (body weight, age, sex, race, ethnicity, or renal, or hepatic impairment) on PK parameters were generally within the interindividual PK variability of tirzepatide. In renal impairment study (Study GPGG), no clinically relevant effects on the PK of a single SC dose of 5 mg tirzepatide were observed for participants with normal renal function (≥90 mL/min/1.73 m^2) and in participants with mild (60 to 89 mL/min/1.73 m^2), moderate (30 to 59 mL/min/1.73 m^2), or severe (<30 mL/min/1.73 m^2) renal impairment or end stage renal disease (ESRD). In hepatic impairment study (Study GPGQ), tirzepatide $AUC_{0\text{-}inf}$ and C_{max} was similar across the control and hepatic impairment groups (Child-Pugh A, B, and C) following a single SC dose of tirzepatide 5 mg.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

A total of six Phase 3 clinical studies, 5 conducted globally and 1 conducted in Japan, were evaluated and supported the efficacy of MOUNJARO® (Tirzpatide) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Tirzepatide 5, 10, and 15 mg once-weekly had demonstrated superiority in the primary efficacy endpoint, change baseline in HbA1c (% and mmol/mol) at the primary endpoint visit (40 or 52 weeks) in all 5 global and 1 Japan Phase 3 studies

- when compared to placebo (as monotherapy in Study I8F-MC-GPGK [SURPASS-1]: least squared (LS) mean difference: -1.66%, -1.62%, -1.60%, FAS/mITT; in combination with titrated basal insulin with or without metformin in Study I8F-MC-GPGI [SURPASS-5]: LS mean difference: -1.24%, -1.53%, -1.47%, FAS/mITT; all p<0.001),
- when compared to semaglutide 1 mg once-weekly (in combination with metformin in Study I8F-MC-GPGL [SURPASS-2]: LS mean difference: -0.15%, -0.39%, -0.45%, FAS/mITT; p<0.001),
- when compared to dulaglutide 0.75 mg once-weekly (as monotherapy in Study I8F-JE-GPGO [SURPASS J-mono]: LS mean difference: -0.97%, -1.10%, -1.30%, FAS/mITT; p<0.001),

  Note: currently, the Max dose of dulaglutide approved in Taiwan is 4.5mg QW.
- when compared to titrated basal insulin (insulin degludec in Study I8F-MC-GPGH [SURPASS-3]: LS mean difference: -0.6%, -0.76%, -0.89%, FAS/mITT; insulin glargine in Study I8F-MC-GPGM [SURPASS-4]: LS mean difference: -0.72%, -0.91%, -1.02%, FAS/mITT; all p<0.001).

2.4.2 Safety Results

The safety database comprised 5415 patients who received tirzepatide in the phase 2 and 3 studies. In the Phase 3 studies, 5119 patients received tirzepatide. Of these, 2375 patients received tirzepatide for at least 1 year, with 535 patients for at least 18 months, and 17 patients for at least 2 years (≥104 weeks).

The safety profile for Tirzpatide were generally consistent with the known safety profile of other products with GLP-1 receptor agonists. Nausea, vomiting, and diarrhea were the most common AEs overall. The rate of gastrointestinal adverse events was dose-dependently higher with tirzepatide compared with placebo. Similar to GLP-1 receptor agonists, hypoglycaemias only occurred in combination with other glucose-lowering drugs, and tirzepatide lowers blood pressure in combination with sulphonylurea or insulin and dose-dependently increases pulse rate. The exposure-adjusted incidence rate (patients per 100 patient-years) for acute pancreatitis in the clinical studies was 0.23 for tirzepatide and 0.11 for pooled comparators. In Study GPGL, the incidence of adjudication-confirmed acute pancreatitis was 0.28% with tirzepatide and 0.64% with semaglutide.

Calcitonin increases were monitored as a potential signal for the development of C-cell hyperplasia and neoplasms. Sixteen tirzepatide-treated patients in the Phase 3 studies had a postbaseline increase in calcitonin ≥50% and an absolute value ≥35 ng/L. It is noted that no calcitonin elevation was observed in the semaglutide 1 mg and dulaglutide 0.75 mg comparator groups of study GPGL and GPGO, respectively. No cases of medullary thyroid carcinoma were identified across the phase 2 and 3 clinical studies.

A cardiovascular (CV) safety meta-analysis based on data from all phase 2 and phase 3 clinical studies was performed to assess the effect of tirzepatide on CV risk. The estimated hazard ratio for the pooled tirzepatide arms versus pooled comparator arms was HR = 0.80, 95% CI (0.57, 1.11) based on a total of 142 MACE events. The cardiovascular meta-analysis excludes an excessive cardiovascular risk.

2.5 Bridging Study Evaluation

PK

Tirzepatide has conducted several clinical studies used to support indication for T2DM, and some of these studies enrolled East Asian populations. Japanese PK data from Phase I study and Phase III Pop PK analysis were used to assess the ethnic sensitivity for tirzepatide PK. From Pop PK analysis, tirzepatide steady-state trough concentrations in Japanese (N=1086) were approximately 17% higher than non-Japanese (N=4716) for each tirzepatide dose (5 mg, 10 mg, and 15 mg QW). The exposure difference may be associated with lower mean body weight in Japanese versus non-Japanese patients but the extent of impact does not warrant dose modification. In addition, model-predicted tirzepatide dose-response at Week 52 for change

from baseline fasting glucose and change from baseline HbA1c showed considerable similarity between Japanese and non-Japanese patients. Overall, no dose adjustment is likely required in the East Asian population.

Clinical

The East Asian data mainly came from the Japanese phase 3 controlled trial (GPGO)、the Japanese phase 3 long-term safety trial (GPGP) and 2 Global phase 3 trials (GPGK and GPGI, Japanese subjects accounting for 17~18.6% of overall population). In addition, the Global phase 3 trial GPGH also included 36 Taiwanese subjects and 36 Korean subjects; the GPGM trial included 30 Taiwanese subjects.

The efficacy of Tirzepatide in East Asian population was demonstrated in the following studies:

- Japanese phase 3 controlled trial (GPGO): a total of 636 subjects were randomized. Tirzepatide 5 mg, 10 mg, and 15 mg were superior to dulaglutide 0.75 mg on mean change from baseline in HbA1c at 52 weeks.
- In the 2 Global phase 3 trials, GPGK and GPGI, the change in HbA1c from baseline to 40 weeks after administration in the tirzepatide group was larger in the Japanese population than in the overall population.

The safety results in the East Asian subpopulation were generally similar to those in the entire study population. The incidence of Nausea、Diarrhea and hypoglycemia AE in East Asian subpopulation were lower than the overall population. However, the heart rate increases were higher in Japanese patients compared to non-Japanese patients. Given that the proposed tirzepatide labeling recommends a gradual dose titration to an effective, tolerable dose, it is acceptable that no dose adjustment was needed for East Asian population.

In summary, the submitted PK, clinical efficacy and safety data can support the proposed dosage of Tirzepatide for the claimed indication for Taiwanese patients. No further bridging study was needed.

2.6 Conclusion

Based on review of the submitted package, the review team considered Tirzpatide demonstrates a favorable risk-benefit profile with adequate evidence to support regular approval for the following indication:

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

3. Post-Marketing Requirements

1. Submit the interim and final report of the “medullary thyroid carcinoma registry-based case series study” as requested by US FDA.