Medicines & Healthcare products Regulatory Agency

Public Assessment Report

National Procedure

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

Tirzepatide

PLGB 14895/0340-0345

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LAY SUMMARY

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

This is a summary of the Public Assessment Report (PAR) for Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg KwikPen solution for injection in pre-filled pen. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Mounjaro KwikPen in this lay summary for ease of reading.

For practical information about using Mounjaro KwikPen, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Mounjaro KwikPen and what is it used for?

These applications are full-dossier applications. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

The applications are line extensions of the existing products Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen (PLGB 14895/0317-18 and PLGB 14895/0320-0323).

Mounjaro KwikPen is used to treat adults with type 2 diabetes mellitus:
- on its own when the patient can't take metformin (another diabetes medicine).
- with other medicines for diabetes when they are not enough to control the patient's blood sugar levels. These other medicines may be medicines taken by mouth and/or insulin given by injection.

It is important that the patient continues to follow the advice on diet and exercise given to them by their doctor, pharmacist or nurse.

Mounjaro KwikPen is also used together with reduced-calorie diet and increased physical activity for weight loss and to help keep the weight under control in adults, who have:
- a BMI of 30 kg/m² or greater (obesity) or
- a BMI of at least 27 kg/m² but less than 30 kg/m² (overweight) and weight-related health problems (such as prediabetes, type 2 diabetes, high blood pressure, abnormal levels of fats in the blood, breathing problems during sleep called 'obstructive sleep apnoea' or a history of heart attack, stroke or blood vessel problems)

BMI (Body Mass Index) is a measure of weight in relation to height.

How does Mounjaro KwikPen work?

Mounjaro KwikPen contains an active substance called tirzepatide. When used to treat adults with type 2 diabetes mellitus, Mounjaro KwikPen reduces the level of sugar in the body only when the levels of sugar are high. When used for weight loss and weight maintenance in adults, Mounjaro KwikPen primarily works by regulating the appetite, giving the patient a

sense of satiety ('fullness'), making them feel less hungry and experience less food cravings. This will help the patient eat less food and reduce their body weight.

How is Mounjaro KwikPen used?
The pharmaceutical form of this medicine is a solution for injection and the route of administration is subcutaneous injection (injection under the skin).

Each Mounjaro KwikPen contains 4 doses of either 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg of Mounjaro.

The starting dose is 2.5 mg once a week for four weeks. After four weeks the patient's doctor will increase the dose to 5 mg once a week.

The patient's doctor may increase the patient's dose by 2.5 mg increments to 7.5 mg, 10 mg, 12.5 mg or 15 mg once a week if needed. In each case the patient's doctor will tell their patient to stay on a particular dose for at least 4 weeks before going to a higher dose.

The dose should not be changed unless the patient's doctor tells them to.

For further information on how Mounjaro KwikPen is used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Mounjaro KwikPen have been shown in studies?
Mounjaro KwikPen is a line extension of the existing products Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen (PLGB 14895/0317-18 and PLGB 14895/0320-0323). The data submitted previously for Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen, along with a study to determine that Mounjaro KwikPen is bioequivalent to the existing product, is sufficient to demonstrate that Mounjaro KwikPen shows a benefit in the indications listed. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Mounjaro KwikPen?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.ukor search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Mounjaro KwikPen are line extensions of the existing products Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen, their benefits

and possible side effects are taken as being the same as Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen.

Why was Mounjaro KwikPen approved?
It was concluded that, as Mounjaro KwikPen are line extensions of Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen, the indications and side effects observed with Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen are applicable to Mounjaro KwikPen. Therefore, the MHRA decided that, as for Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen, the benefits are greater than the risks and recommended that Mounjaro KwikPen can be approved for use.

Mounjaro KwikPen has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Mounjaro KwikPen?"

What measures are being taken to ensure the safe and effective use of Mounjaro KwikPen?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Mounjaro KwikPen. The RMP details the important risks of Mounjaro KwikPen, how these risks can be minimised, any uncertainties about Mounjaro KwikPen (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Mounjaro:

Important identified risks:
- None

Important potential risks:
- Medullary thyroid cancer
- Pancreatic malignancy
- Diabetic retinopathy complications

Missing information
- Use in pregnancy and lactation
- Medication errors related to vial presentation
- Significant active or unstable major depressive disorder or other sever psychiatric disorder
- Off-label use in patients who do not meet the criteria for treatment (weight management)

Additional pharmacovigilance activities are planned to evaluate the potential risks of medullary thyroid cancer, pancreatic cancer and diabetic retinopathy.

Additional pharmacovigilance activities are also planned to evaluate the use of Mounjaro in pregnancy and during breastfeeding. This includes a patient registry to collect data on pregnant patients and pregnancy related outcomes, an observational study of exposure during pregnancy and a study of the levels of Mounjaro found in breast milk of post-partum lactating females.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Mounjaro KwikPen are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Mounjaro KwikPen
Marketing authorisations were granted in Great Britain (GB, consisting of England, Scotland and Wales) on 25 January 2024.

The full PAR for Mounjaro KwikPen follows this summary.

This summary was last updated in February 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg KwikPen solution for injection in pre-filled pen (PLGB 14895/0340-0345) could be approved.

The products are approved for the following indications:
For the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

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

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

- ≥ 30 kg/ m2 (obesity) or
- ≥ 27 kg/m2 to < 30 kg/m2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).

The products contain the active substance tirzepatide. Tirzepatide is a long-acting dual GIP and GLP-1 receptor agonist. Both receptors are present on the pancreatic α and β endocrine cells, brain, heart, vasculature, immune cells (leukocytes), gut and kidney. GIP receptors are also present on adipocytes.

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

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

Tirzepatide lowers body weight and body fat mass. The mechanisms associated with body weight and body fat mass reduction involve decreased food intake through the regulation of appetite and modulation of fat utilisation. Clinical studies show that tirzepatide reduces energy intake and appetite by increasing feelings of satiety (fullness), decreasing feelings of hunger, and decreasing food cravings.

These applications were approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), as full-dossier applications. These applications are for line extensions of the existing products Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen (PLGB 14895/0317-18 and PLGB 14895/0320-0323.

In line with the legal requirements for children's medicines, the applications included a licensing authority decision on the agreement of paediatric investigation plans (PIPs) (MHRA-100820-PIP01-22 and MHRA-100447-PIP01-22-M02). At the time of the submission of the applications the PIPs were not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations were granted in Great Britain (GB, consisting of England, Scotland and Wales) on 25 January 2024.

II QUALITY ASPECTS

II.1 Introduction

These products consist of multiple-dose pre-filled pens containing 4 doses of 0.6 ml solution which can be administered.

Each dose (0.6 ml) contains either 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg or 15 mg of tirzepatide.

In addition to tirzepatide, these products also contain the following excipients:

Sodium phosphate dibasic heptahydrate
Sodium chloride
Concentrated hydrochloric acid, and sodium hydroxide (for pH adjustment)
Glycerol
Phenol
Benzyl Alcohol
Water for injections

Each pre-filled KwikPen contains 3 ml of solution and 2.4 ml of solution that can be administered. The finished products are packaged in a pack size of 1 and 3 pre-filled KwikPens. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

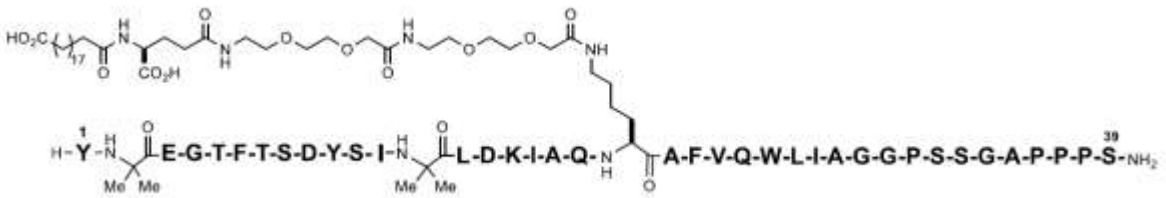
II.2 ACTIVE SUBSTANCE

rINN: Tirzepatide

Chemical Name: L-Serinamide, L-tyrosyl-2-methylalanyl-L-α-glutamylglycyl-L-threonyl-Lphenylalanyl-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-N6-[(22S)-22,42-dicarboxy-1,10,19,24-tetraoxo-3,6,12,15-tetraoxa-9,18,23-triazadotetracont-1-yl]-Llysyl-L-alanyl-L-phenylalanyl-L-valyl-L-glutaminyl-L-tryptophyl-L-leucyl-L-isoleucyl-Lalanylglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl

Molecular Formula: $C_{225}H_{348}N_{48}O_{68}$

Chemical Structure:



Molecular Weight: 4810.52 Da (monoisotopic mass)
4813.45 Da (average mass IUPAC 2007)

Appearance: White to practically white solid

Solubility: Freely soluble in 5 mM phosphate buffer pH 7.0 at 25°C

Tirzepatide is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished products.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 9 months, with the following storage conditions is acceptable:

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

Mounjaro may be stored unrefrigerated for up to 30 days at a temperature not above 30 ºC and then the pre-filled KwikPen must be discarded.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As these applications are for line extensions of the existing products Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen (PLGB 14895/0317-18 and PLGB 14895/0320-0323), the non-clinical data are identical to those submitted previously.

III.2 Pharmacology
No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a line extension of an already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
These applications are for line extensions of the existing products Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen (PLGB 14895/0317-18 and PLGB 14895/0320-0323). With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study.

Study I8F-MC-GPIP

This study was a multicentre, open-label, randomised, 2-period, 2-sequence, crossover study comparing the multi-dose test product, Mounjaro 5 mg KwikPen solution for injection in pre-filled pen, versus the existing single dose product, Mounjaro 5 mg solution for injection in pre-filled pen, in healthy subjects.

Subjects were administered a single dose of 5 mg of test or reference product, administered by subcutaneous injection. Blood samples were taken pre-dose and up to 480 hours post dose, with a washout period of 35 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1. Statistical Analyses of the Primary Pharmacokinetic Parameters

Parameter	Treatment	n*a	Geometric least squares mean (90% CI)*b	Ratio of geometric least squares mean (MUPFP:SDP) (90% CI)*b
AUC(0-infinity) (ng.h/mL)	5 mg tirzepatide SC (SDP)	62	126787 (125205, 128388)	
	5 mg tirzepatide SC (MUPFP)	62	120155 (118657, 121673)	0.948 (0.931, 0.965)
AUC(0-tlast) (ng.h/mL)	5 mg tirzepatide SC (SDP)	62	124649 (123089, 126228)	
	5 mg tirzepatide SC (MUPFP)	62	117535 (116064, 119024)	0.943 (0.926, 0.960)
Cmax (ng/mL)	5 mg tirzepatide SC (SDP)	62	648.5 (632.4, 665.1)	
	5 mg tirzepatide SC (MUPFP)	62	524.2 (511.2, 537.6)	0.808 (0.780, 0.838)

Abbreviation: AUC(0-infinity) = area under the concentration versus time curve from zero to infinity; AUC(0-tlast) = area under the concentration versus time curve from time zero to last timepoint with a measurable concentration; Cmax = maximum observed drug concentration; CI = Confidence Interval; MUPFP = Multi-use pre-filled pen; PK = Pharmacokinetics; n = number of observations for analysis; SC = Subcutaneous; SDP = Single-dose pen. a* For each PK parameter, only include participants who received all study interventions, and have evaluable PK parameter value for both treatment periods. b* Linear Fixed-effects Model: log(parameter value) = Treatment + Sequence + Period + Subject(Sequence) + Random Error, where Subject(Sequence) is fitted as a fixed effect. Results were presented after back-transformed.

Table 2. Statistical Analyses of the Variability of the Pharmacokinetic Parameters

Parameter	Intra-subject CV%*a
AUC(0-infinity) (ng.h/mL)	5.9
AUC(0-tlast) (ng.h/mL)	5.9
Cmax (ng/mL)	11.9

Abbreviation: AUC(0-infinity) = area under the concentration versus time curve from zero to infinity; AUC(0-tlast) = area under the concentration versus time curve from time zero to last timepoint with a measurable concentration; Cmax = maximum observed drug concentration; CV% = geometric coefficient of variation; PK = Pharmacokinetics.
a* Linear Fixed-effects Model: log(parameter value) = Treatment + Sequence + Period + Subject(Sequence) + Random Error, where Subject(Sequence) is fitted as a fixed effect. Results were presented after back-transformed.

The median difference of tmax of tirzepatide was 12 hours between MDPFP and SDP. tmax was attained later when tirzepatide was administered by a MDPFP versus when administered by an SDP.

Table 3. Statistical Analyses of Pharmacokinetic Parameter tmax by Device

Parameter	Treatment	n*a	Median (Min, Max)	Median of differences (MUPFP-SDP) (90% CI)*b	P-value*c
tmax (h)	5 mg tirzepatide SC (SDP)	62	12.00 (7.97, 168.08)		
	5 mg tirzepatide SC (MUPFP)	62	36.00 (8.00, 144.00)	12.13 (6.03, 18.13)	<.0001

Abbreviation: CI = Confidence Interval; h = hour; Max = Maximum; Min = Minimum; MUPFP = Multi-use pre-filled pen; n = number of observations for analysis; PK = Pharmacokinetics; SC = Subcutaneous; SDP = Single-dose pen; tmax = time of maximum observed drug concentration. a* Only include participants who received all study interventions, and have evaluable PK parameter value for both treatment periods. b* Median of difference and 90% CI are obtained from Hodges-Lehmann estimate of location shift in PROC NPAR1WAY. c* P value is from Wilcoxon ranked-sum test.

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals for AUC(0-tlast) and AUC(0-∞) were within the specified limits to show bioequivalence between the test product and the reference product. However, the Test/Reference ratios and their 90% confidence intervals for peak exposure as measured by

Cmax were not within the specified limits to show bioequivalence between the test product and the reference product.

The median difference in tmax of 12 hours between the test and reference products was also noted, although this was not part of the bioequivalence evaluation.

In order to address the issue of the lower Cmax with the new multi-dose pre-filled pen (MDPFP; Mounjaro KwikPen) compared to the already authorised single dose pen (SDP), the Applicant submitted further analyses, which also considered the findings of previous pharmacokinetic (PK) studies carried out to support the Mounjaro clinical development.

Comparison and Analyses of Pharmacokinetics and Exposure-Response Relationships across Studies
The PK parameters and exposure metrics for administration of tirzepatide with MDPFP and SDP in Study GPIP were compared to the results from the biopharmaceutic Phase 1 studies (I8F-MC-GPGS [GPGS]) and I8F-MC-GPHI [GPHI]) supporting the type 2 diabetes mellitus (T2DM) program.

The potential efficacy and tolerability associated with MDPFP usage in individuals with T2DM were evaluated by comparing the exposure from Study GPIP to previously established exposure-response relationships for reduction in fasting glucose (FG) and HbA1c, reduction in body weight, and prevalence of nausea in participants with T2DM.

Study I8F-MC-GPGS:
This was a single-centre, open-label, randomised 2-period, 2-sequence, crossover study with healthy participants and compared the PK of a single dose of tirzepatide 5 mg administered SC through an autoinjector (SDP) versus a pre-filled syringe (PFS).

Tirzepatide exposure following administration of a 5-mg dose using SDP was similar to that following PFS, as demonstrated by AUC and Cmax GLSM ratios and 90% CI within the interval of 0.80 to 1.25.

Study I8F-MC-GPHI:
This was a single-centre, open-label, 3-period, 3-sequence, randomized, crossover study with healthy participants in 2 body mass index groups (low [18.5 to 27.0 kg/m2] and high [27.1 to 45.0 kg/m2]) and investigated administration of tirzepatide with the SDP device at the abdomen, thigh, and upper arm injection sites.

Tirzepatide exposure, defined as AUC(0-∞) and Cmax, following administration of a 5-mg dose to the upper arm or thigh injection site was similar to that attained following administration to the abdomen injection site, i.e., the 90% CI for the GLSM ratios of each comparison fell within the interval of 0.80 to 1.25.

Comparison of Noncompartmental PK Analysis Exposure Parameters from Studies GPIP, GPGS, and GPHI
Data on the tirzepatide concentrations over time from Studies GPIP, GPGS, and GPHI were analysed using standard noncompartmental methods of analysis.

Compared with the curves associated with SDP or PFS administration, the shape of the tirzepatide concentration versus time curve associated with PFP delivery appears to have slightly lower concentrations in the initial time after dosing, i.e., within the time interval up

to 48 hours post-dose and higher concentrations, thereafter, suggesting that the total extent of exposure is similar and only the rate of absorption may be slightly lower with PFP delivery.

Table 4 presents a summary of the exposure parameters AUC(0-∞) and Cmax calculated from noncompartmental PK analysis.

The reported PK parameters from Study GPIP were within the range of values reported for Studies GPGS and GPHI.
When evaluating by device, the tirzepatide AUC and Cmax were comparable between:
- PFP in Study GPIP and SDP in Studies GPIP, GPGS, and GPHI.
- PFP in Study GPIP and PFS in Study GPGS.

Table 4. Summary of exposure parameters from noncompartmental analysis of a single dose of tirzepatide 5 mg subcutaneously in healthy participant studies GPIP, GPGS and GPHI.

	Geometric mean (CV%)					
Study[a]	GPIP	GPIP	GPGS	GPGS	GPHI (low BMI)[b]	GPHI (high BMI)[b]
Device	PFP	SDP	SDP	PFS	SDP	SDP
N	62	65	42	44	27	27
$AUC_{(0-\infty)}$ (ng·h/mL)	119000[c] (22%)	126000 (22%)	101000 (18%)	104000[e] (18%)	126000 (15%)	100000 (27%)
C_{max} (ng/mL)	524 (27%)	647 (31%)	530 (25%)	556 (22%)	670 (19%)	544 (26%)
$t_{1/2}$[d] (hours)	126[c] (81.5 – 186)	122[f] (39.0 – 178)	122 (96.8 – 152)	121[g] (97.9 – 153)	132 (109 – 155)	125 (103 – 168)

Abbreviations: $AUC_{(0-\infty)}$ = area under the concentration versus time curve from time 0 to infinity; BMI = body mass index; C_{max} = maximum observed drug concentration; CV = coefficient of variation; GPGS = Study I8F-MC-GPGS; GPHI = Study I8F-MC-GPHI; GPIP = Study I8F-MC-GPIP; N = number of participants; PFP = fixed, multi-dose prefilled pen; PFS = prefilled syringe; SC = subcutaneous; SDP = single-dose pen; $t_{1/2}$ = half-life.

[a] The arithmetic mean (standard deviation) baseline body weight was 71.2 kg (11.3) [GPIP], 72.0 kg (11.5) [GPGS], 73.8 kg (8.39) [GPHI, low BMI], and 96.5 kg (17.0) [GPHI, high BMI].
[b] Participants with BMI 27 kg/m^2 and BMI > 27 kg/m^2 were grouped as low BMI and high BMI, respectively.
[c] N = 61.
[d] Geometric mean (minimum – maximum).
[e] N = 60.
[f] N = 64.
[g] N = 42.

Population PK Analysis of the Influence of Device on Tirzepatide PK

A population PK analysis focusing on the tirzepatide concentrations from the biopharmaceutic Studies GPIP, GPGS, and GPHI was performed to evaluate the influence of PFP device on tirzepatide PK.

Previously, a robust population PK model was developed using the nonlinear mixed effects modeling softwareand pooled data from Phase 1, 2, and 3 studies supporting the initial T2DM application (5802 participants, 39644 observations). The impact of delivery devices on tirzepatide PK was evaluated as part of the covariate screening within the T2DM population PK model development. No statistically or clinically significant differences in PK were detected between the devices used to support the T2DM program (SDP and PFS) and these results were consistent with noncompartmental analysis results from Study GPGS.
The established population PK model supporting the initial T2DM application was used as the base model for the analysis of Studies GPIP, GPGS, and GPHI. The base model has 2 compartments with first-order absorption and interindividual variability on ka, clearance (CL), and central volume of distribution (Vc). The bioavailability parameter was fixed to 0.8

based on the results from the Phase 1 bioavailability Study (I8F-MC-GPGE). Body weight-based allometric parameters were included as fixed values on clearance and volume of distribution parameters based on the previously established tirzepatide population PK model.

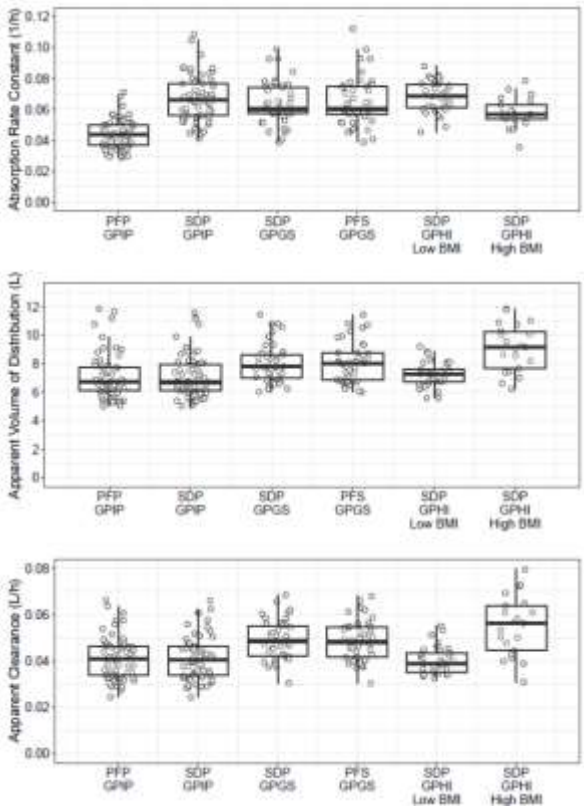
PFP was a statistically significant covariate on the absorption rate constant (ka). The estimate of ka following administration of tirzepatide with PFP was 35% lower than the estimate of ka following administration with SDP.

No difference between delivery through PFP versus SDP or PFS was detected for the PK parameters of bioavailability, clearance, or volume of distribution in the population PK model, and these findings were consistent with the comparison of noncompartmental analysis results that showed comparable extent of exposure (AUC) between delivery devices.

The tirzepatide PK parameter estimates from the population PK analysis of Studies GPIP/GPGS/GPHI were consistent with the T2DM population PK model parameter estimates (Table 5). Figure 1 and Figure 2 show a summary of the model-based post hoc PK and exposure parameters for Studies GPIP, GPGS, and GPHI. The range of values for tirzepatide exposure overlap between studies and devices.

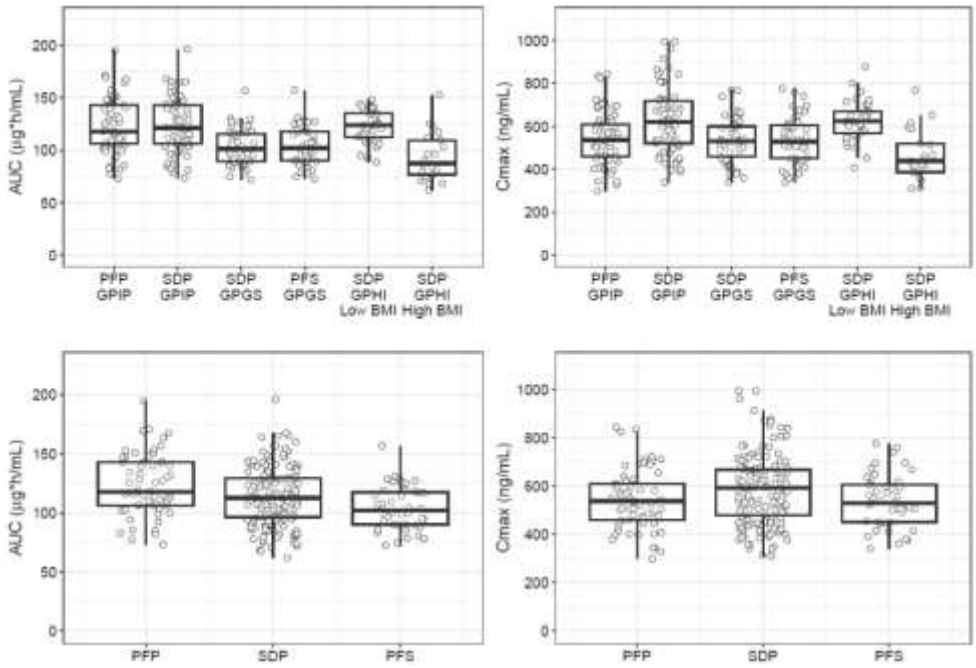
The difference between the model-estimated ka associated with PFP versus SDP delivery has minimal impact on the metrics of tirzepatide exposure (AUC and Cmax).

Figure 1. Population model-based post hoc PK parameters stratified by study and device



Abbreviations: BMI = body mass index; GPGS = Study I8F-MC-GPGS; GPHI = Study I8F-MC-GPHI; GPIP = Study I8F-MC-GPIP; High BMI = participants with BMI >27 kg/m2 ; low BMI = participants with BMI ≤27 kg/m2 ; PFP = fixed, multi-dose pre-filled pen; PFS = pre-filled syringe; PK = pharmacokinetic(s); SDP = single-dose pen. Note: The middle line in each boxplot represents the median; the top and bottom margins of the boxplot represent the 75th and 25th percentiles; the whiskers extend up to ±1.5 times the interquartile range. The open symbols represent the individual post hoc PK parameter values.

Figure 2. Population model-based post hoc AUC (left) and Cmax (right) stratified by study and device (top) and device alone (bottom).



Abbreviations: AUC = area under the concentration versus time curve; BMI = body mass index; Cmax = maximum observed drug concentration; GPGS = Study I8F-MCGPGS; GPHI = Study I8F-MC-GPHI; GPIP = Study I8F-MC-GPIP; High BMI = participants with BMI >27 kg/m2 ; Low BMI = participants with BMI ≤27 kg/m2 ; PFP = fixed, multi-dose pre-filled pen; PFS = pre-filled syringe; PK = pharmacokinetics; SDP = single-dose pen. Note: The middle line in each boxplot represents the median; the top and bottom margins of the boxplot represent the 75th and 25th percentiles; the whiskers extend up to ±1.5 times the interquartile range. The open symbols represent the individual post hoc PK parameter values.

Table 5. Tirzepatide Population PK model parameters

Parameter	GPIP/GPGS/GPHI Model Estimate Median (95% CI)[a]	T2DM Model Estimate Median (95% CI)[a]
	N =164 , nobs = 3517	N = 5802, nobs = 39644
Bioavailability (F, fraction)	0.8 fixed	0.8 fixed
Absorption rate constant[b] (ka, 1/h)	0.0434 [PFP] 0.0433 (0.0339, 0.0550) 0.0664 [SDP] 0.0661 (0.0565, 0.0770)	0.0373 0.0370 (0.0289, 0.0460)
Clearance[c] (CL, L/h/70 kg)	0.0337 0.0337 (0.0328, 0.0345)	0.0329 0.0329 (0.0313, 0.0342)
Intercompartmental clearance[c] (Q, L/h/70kg)	0.254 0.252 (0.227, 0.284)	0.126 0.125 (0.101, 0.144)
Central volume of distribution[d] (Vc, L/70kg)	2.07 2.06 (1.62, 2.50)	2.47 2.46 (2.05, 2.92)
Peripheral volume of distribution[d] (Vp, L/70kg)	4.55 4.55 (4.19, 4.90)	3.98 3.98 (3.56, 4.21)

Interindividual variability (CV%)		
Ka	20.6% 20.3 (17.3, 23.3)	22.5% 22.1 (14.9, 28.7)
CL	15.8% 15.7 (14.1, 17.4)	14.2% 14.2 (13.7, 14.7)
Vc	49.6% 49.5 (40.4, 63.1)	49.0% 49.5 (38.3, 62.3)
Residual variability		
Proportional (%)	11.6% 11.5 (11.0, 12.1)	20.6% 20.6 (20.3, 21.0)

Abbreviations: BW = body weight; CI = bootstrap-derived confidence interval; CL = clearance; CV = coefficient of variation; GPGS = Study I8F-MC-GPGS; GPHI = Study I8F-MC-GPHI; GPIP = Study I8F-MC-GPIP; N = number of participants; nobs = number of observations; PFP = fixed, multi-dose prefilled pen; PK = pharmacokinetics; SDP = single-dose pen; T2DM = type 2 diabetes mellitus; Vd = volume of distribution.

[a] Median and 95% CI derived from bootstrap analysis.

[b] ika = tvka * (BW/70)^-0.558 where ika is an individual's ka, tvka is the population ka, and BW is an individual's BW. The described structure was used only in the GPIP/GPGS/GPHI model.

[c] iCL = tvCL * (BW/70)^0.8 where iCL is an individual's CL, tvCL is the population CL, and BW is an individual's BW. The described structure was applied to CL and Q in both the GPIP/GPGS/GPHI and T2DM models.

[d] iVd = tvVd * [(fat free mas + fat mass * Θ_9)/70]^1 where iVd is an individual's Vd, tvVd is the population Vd, fat free mass is an individual's fat free mass, fat mass is an individual's fat mass, and Θ_9 is a fraction. The estimate of Θ_9 was 0.482 in the T2DM model and this value was used in the GPIP/GPGS/GPHI model. The described structure was applied to Vc and Vp in both the GPIP/GPGS/GPHI and T2DM models.

Assessment of Device Impact on Efficacy and Tolerability. Based on Exposure-Response Relationships

The pharmacology of GLP-1 analogs for the treatment of T2DM uses a prolonged t1/2 approach relative to the short t1/2 (approximately 2 minutes) of native GLP-1. Tirzepatide is a QW administered dual GIP and GLP-1-RA with a mean t1/2 of approximately 5 days, which enables sustained therapeutic exposure during treatment. In the understanding of the clinical pharmacology of tirzepatide, the extent of exposure with repeated dosing (steady-state AUC[0-tau]) was related to the efficacy responses (HbA1c and body weight).
Peak concentrations during the initiation and the early period of treatment were related to GI tolerability, a known tolerability concern of the incretin class of agents. Starting treatment on lower doses and escalating dose levels in smaller increments reduced the incidence and severity of GI events. Doses higher than 5 mg were poorly tolerated in Phase 1 Study GPGA, resulting in a 5-mg dose being considered as the maximum tolerated dose when administered as a single dose.

Subsequently in Phase 2 Study, GPGB, doses higher than 5 mg were attained only by dose escalation with a starting dose of 5 mg.

Robust PK/PD models describing the relationship between tirzepatide concentrations and the key efficacy endpoints of HbA1c and body weight and the tolerability index of nausea prevalence were developed to support the initial T2DM application.

To evaluate the potential impact of tirzepatide exposure on efficacy and tolerability, the tirzepatide exposure metrics observed after a single 5-mg SC dose in Study GPIP were scaled to steady-state values.

Table 6 presents a summary of the single-dose exposure metrics and projected steady-state exposure metrics for Study GPIP.

Table 6. Predicted stead-state exposure metrics based on observed exposure after a single dose of tirpezepatide 5 mg in Study GPIP.

Parameter	Device	Single Dose 5 mg	Steady-State 5 mg QW
AUC[a] (ng·h/mL)	PFP	119000	119000
	SDP	126000	126000
C_{max}[b] (ng/mL)	PFP	524	891
	SDP	647	1100

Abbreviations: AUC = area under the concentration versus time curve; $AUC_{(0-\infty)}$ = AUC from time 0 to infinity; $AUC_{(0\text{-tau})}$ = AUC over one dosing interval where 168 hour is the dose interval for QW tirzepatide; C_{max} = maximum observed drug concentration; PFP = fixed, multi-dose prefilled pen; QW = once weekly; SDP = single-dose pen.

[a] The $AUC_{(0-\infty)}$ after a single dose is equivalent to the $AUC_{(0\text{-tau})}$ at steady state for tirzepatide QW administration.

[b] The C_{max} after a single dose is scaled to steady state by multiplying by 1.7, the accumulation index for tirzepatide QW administration.

Simulations of the steady state exposure have also been performed and show what appears to be a reduced difference on multiple dosing. There is overlap between the two formulations.

Table 7. Summary of Simulated Steady-State Cmax Following Administration of Once-weekly Tirzepatide with Reference or Test Formulations

	Steady-State C_{max} (ng/mL) Median [5th percentile, 95th percentile]	
Tirzepatide Dose (mg)	**Reference (SDP)**	**Test (multi-dose PFP)**
5	860 (560, 1440)	790 (516, 1310)
10	1840 (1180, 3230)	1690 (1080, 2850)
15	2840 (1800, 4960)	2600 (1640, 4430)

Abbreviations: C_{max} = maximum concentration; PFP = pre-filled pen; SDP = single-dose pen.

Exposure-Response Relationships for Efficacy.

Fasting Glucose (FG)-HbA1c

FG and HbA1c data from multiple Phase 2 and 3 studies were used to characterize the PK/PD relationship.

The time course of HbA1c was driven by the effect of tirzepatide on FG concentration through a linked concentration-response model that fitted both FG and HbA1c data jointly. The estimated t1/2 turnover of HbA1c was 3 weeks, which corresponded to the attainment of steady state after 3 to 4 months of glucose and drug exposure, and this was consistent with generally accepted understanding of haemoglobin physiology. Average steady-state tirzepatide concentrations following maintenance doses of 5, 10, and 15 mg QW ranged from 491 to 1470 ng/mL (approximately equivalent to AUC[0-tau] of 82500 to 247000 ng/mL·h) and resulted in 74% to 89% of maximal glycaemic effect.

The projected steady-state exposures (AUC and Cmax) from Study GPIP for both PFP and SDP delivery fall within the model-predicted range of exposures after 40 weeks of treatment with 5, 10, and 15 mg QW tirzepatide in Phase 3 Studies GPGI, GPGK, and GPGM and these exposures were associated with significant observed and model-predicted glycemic efficacy.

Body weight

Body weight data from multiple Phase 2 and 3 studies were used to build the PK/PD model.

A sequential PK/PD modelling approach was used to characterise the effect of tirzepatide on body weight reduction. An indirect response model was used to account for a delay in the effect of tirzepatide in reducing body weight. The typical 'half-life' for weight loss was estimated to be about 9 weeks. This means that it would take about 45 weeks of exposure to tirzepatide concentrations to get to a new steady state of body weight. There is a clear exposure-response relationship between tirzepatide dose and body weight reduction. Average steady-state tirzepatide concentrations following maintenance doses of 5, 10, and 15 mg QW ranged from 491 to 1470 ng/mL (approximately equivalent to AUC[0-tau] of 82500 to 247000 ng/mL·h) and resulted in model-predicted percent change from baseline weight reduction at 40 weeks of -6.9%, -9.9%, and -12.5%, respectively.

The projected steady-state exposures (AUC and Cmax) from Study GPIP for both PFP and SDP delivery fall within the range of model-predicted exposures after 40 weeks of treatment with 5, 10, and 15 mg QW tirzepatide in Phase 3 Studies GPGI, GPGK, and GPGM and these exposures were associated with clinically relevant observed and model-predicted body weight reduction.

Therefore, considering the totality of evidence, the small differences in Cmax observed when comparing the PFP with the SDP in the crossover Study GPIP are not clinically relevant for efficacy of QW tirzepatide.

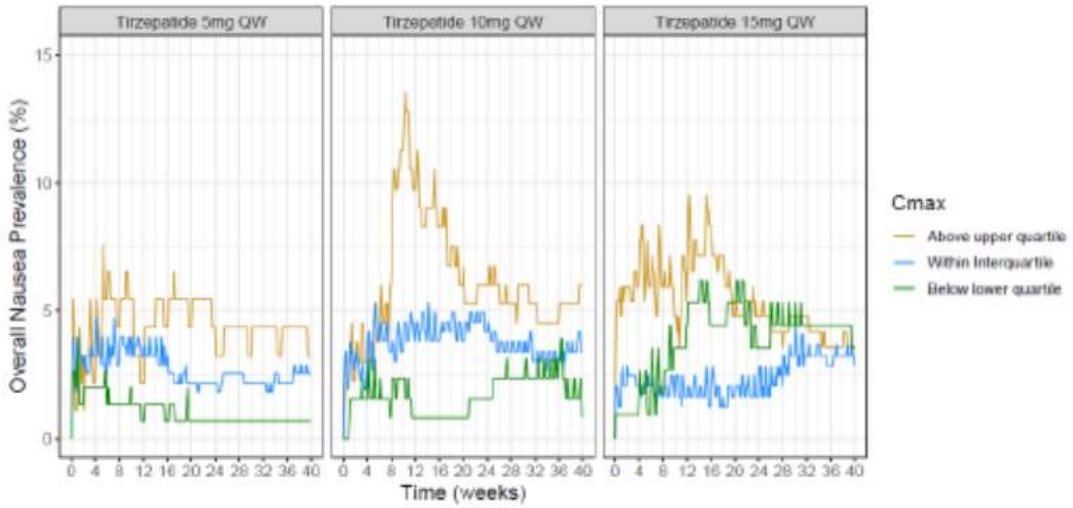
Exposure-Response Relationships for Tolerability
Reports of nausea symptoms collected from multiple Phase 2 and 3 studies were used to build the PK/PD models for GI tolerability.

A sequential modelling approach was taken to fit individual patient's PK time course with the occurrence of nausea. A discrete-time Markov model was used to estimate transition probabilities between adverse event states and assess the impact of tirzepatide exposure and potential covariates on these probabilities.

The implementation of stepwise dose-escalation scheme starting at 2.5-mg dose for 4 weeks, followed by increases in doses by 2.5-mg increments every 4 weeks to attain maintenance dose levels of 5, 10, and 15 mg in Phase 3 studies, mitigated the incidence of GI adverse events, especially at the 10- and 15-mg doses. A majority of the events of nausea at the 5-, 10-, and 15-mg dose levels were reported during the dose-escalation phase, and these events decreased with time, and the incidence rate was <10% once steady-state concentrations for the maintenance doses were attained, i.e., after 24 weeks.

To illustrate the impact of Cmax on the prevalence of nausea, the model-predicted exposure from three Phase 3 studies (Studies GPGI, GPGK, and GPGM) was stratified by quartiles, and the observed prevalence of nausea over time for the bottom quartile, interquartile, and top quartile of exposure was plotted. Generally, lower values of Cmax are associated with better tolerability as indicated by the decreased prevalence of nausea.

Figure 3. Observed nausea prevalence during 40 weeks of treatment with tirpezatide 5, 10 and 15 mg QW in Phase 3 studies stratified by quartiles of Cmax.



Abbreviations: C_{max} = maximum observed drug concentration; Phase 3 studies = Study I8F-MC-GPGI, Study I8F-MC-GPGK, and Study I8F-MC-GPGM; QW = once weekly.

The tirzepatide exposure as defined by AUC(0-tlast) and AUC(0-∞) in Study GPIP was well within prespecified criteria and are the critical exposure parameters when considering efficacy. While tirzepatide peak concentrations may show a more direct correlation with GI tolerability, the differences in tirzepatide Cmax between PFP and SDP delivery observed in Study GPIP have a low likelihood of resulting in additional tolerability or safety concerns based on the current understanding of exposure-response relationships.

Pharmacokinetic Conclusion

Tirzepatide administered using a multi-dose PFP (KwikPen) is expected to result in comparable efficacy to the SDP (autoinjector) because both AUC parameters met the bioequivalence criteria in Study GPIP and the tirzepatide exposure metrics in Study GPIP were comparable to the exposure data from Phase 1, 2, and 3 studies supporting the initial T2DM application.

While the lower bound of 90% CI for Cmax did not meet the prespecified criteria, this excursion (lower Cmax) is not likely to have any clinically significant effect. It is not expected to result in additional concerns over safety and tolerability and continues to maintain a favourable benefit-risk assessment of tirzepatide treatment.

The arguments for AUC as the important parameter based on the PKPD understanding are understood: The turnover rate for key pharmacodynamic (PD) endpoints of HbA1c and body weight reduction are known to be slow and the PK/PD model estimated typical half-life for weight loss was about 9 weeks. Simulations performed with the PKPD model for fasting glucose show the relationship between tirzepatide concentrations and fasting glucose and that the small differences in Cmax for the multi-dose PFP versus the SDP are not expected to result in any discernible clinical difference in PD effect.

As the additional (2.5 mg, 7.5 mg, 10 mg and 15 mg) strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strengths.

IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

IV.4 Clinical efficacy

No new efficacy data have been submitted for these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance measures have been proposed:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
Medullary thyroid cancer	**Routine risk minimisation measures:** • SmPC Section 5.3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Cancer/Neoplasm follow-up form • Hypocalcaemia, Hypokalaemia, Hypomagnesaemia, Hypophosphataemia follow-up form **Additional pharmacovigilance activities:** I8F-MC-B013: A Medullary Thyroid Carcinoma Database Linkage Study: The primary objective to estimate the incidence of medullary thyroid carcinoma among patients who are exposed to GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, as compared to an unexposed matched comparator cohort using incidence rate ratios and 95% CI. The secondary objectives are to • systematically monitor the annual incidence of MTC in adults (18 years of age and older) in the US for identification of any possible increase related to the introduction of GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, into the US market, and • characterise patients exposed to GLP-1 RAs and the GIP/GLP-1 RA tirzepatide, and unexposed matched comparator cohorts using demographic characteristics and other clinical characteristics, selected prescription medications dispensed during the baseline period, and duration of GLP-1 RA (including GIP/GLP-1 RA) use.
Pancreatic malignancy	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Cancer/Neoplasm follow-up form **Additional pharmacovigilance activities:** • I8F-MC-B011: Tirzepatide Pancreatic Malignancy Study: This is a retrospective non-interventional cohort study.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		The primary objectives of this study are to • estimate the incidence rate of pancreatic cancer among new users of tirzepatide • compare the incidence rate of pancreatic cancer among new users of tirzepatide to patients who are new users of other incretin-based therapies, and • compare the incidence rate of pancreatic cancer among new users of tirzepatide to patients who are new users of non-incretin-based therapies. The secondary objective of this study is to describe baseline characteristics (including demographics, lifestyle variables, medical conditions, medications) among patients who are new users of tirzepatide and patients who are new users of other incretin-based therapies and non-incretin-based therapies.
Diabetic retinopathy complications	**Routine risk minimisation measures:** • SmPC Section 4.4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Not applicable **Additional pharmacovigilance activities:** • Protocol Addendum I8F-MC-GPGN This is a retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN) to compare the effect of tirzepatide dose up to 15 mg QW with dulaglutide 1.5 mg QW on DR progression. and to assess the safety of tirzepatide dose up to 15 mg QW when compared with dulaglutide 1.5 mg QW on DR.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing Information		
Use in pregnant and/ or breastfeeding women	**Routine risk minimisation measures:** • SmPC Section 4.6 • PL Section 2 **Additional Risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Maternal and paternal pregnancy exposure data collection follow-up form • Maternal and paternal pregnancy exposure outcome follow-up form • Breast feeding follow-up form **Additional pharmacovigilance activities:** • Prospective pregnancy exposure registry • Observational Cohort Study of Exposure to Tirzepatide During Pregnancy • A Study of Tirzepatide (LY3298176) in Healthy Lactating Females; an 8-week study in post-partum lactating females to assess the pharmacokinetics of tirzepatide in breast milk.
Medication Errors related to vial presentation	**Routine risk minimisation measures:** • SmPC Section 4.2 • PL Section 3 **Additional Risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • None
Significant active or unstable major depressive disorder or other severe psychiatric disorder	**Routine risk minimisation measures:** None **Additional Risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Suicide Attempt or Ideation follow-up form • Death by Suicide follow-up form **Additional pharmacovigilance activities:** None
Off-label use in patients who do not meet criteria for treatment (weight management)	**Routine risk minimisation measures:** • SmPC Section 4.1 • PL Section 1 **Additional Risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL for Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in pre-filled pen (PLGB 14895/0317-18 and PLGB 14895/0320-0323) has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use. The Applicant has justified that additional user testing is not required.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no non-clinical or clinical safety concerns have been identified. Clinical experience with tirzepatide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPCs and PILs for these products are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**