Medicines & Healthcare products Regulatory Agency

Public Assessment Report

National Procedure

Mounjaro 2.5 mg solution for injection in vial
Mounjaro 5 mg solution for injection in vial
Mounjaro 7.5 mg solution for injection in vial
Mounjaro 10 mg solution for injection in vial
Mounjaro 12.5 mg solution for injection in vial
Mounjaro 15 mg solution for injection in vial

Tirzepatide

PLGB 14895/0331-0336

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LAY SUMMARY

Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in vial
Tirzepatide

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 solution for injection in vial. 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 in this lay summary for ease of reading.

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

What is Mounjaro 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 prefilled pen (PLGB 14895/0317-18 and PLGB 14895/0320-0323).

Mounjaro 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.

How does Mounjaro work?
Mounjaro contains an active substance called tirzepatide. Mounjaro reduces the level of sugar in the body only when the levels of sugar are high.

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

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 their 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 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 have been shown in studies?
No additional studies were needed as Mounjaro 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 prefilled 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 prefilled pen is sufficient to demonstrate that Mounjaro shows a benefit in the indications listed.

What are the possible side effects of Mounjaro?
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 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 prefilled 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 prefilled pen.

Why was Mounjaro approved?
It was concluded that, as Mounjaro is a line extension of Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in prefilled 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 prefilled pen are applicable to Mounjaro. 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 prefilled pen, the benefits are greater than the risks and recommended that Mounjaro can be approved for use.

Mounjaro 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?"

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

minimised, any uncertainties about Mounjaro (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Mounjaro:

Summary of Safety Concerns	
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

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

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 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
Marketing authorisations were granted in Great Britain (GB, consisting of England, Scotland and Wales) on 01 September 2023.

The full PAR for Mounjaro follows this summary.

This summary was last updated in November 2023.

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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 solution for injection in vial (PLGB 14895/0331-0336) 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.

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.

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. However, 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 prefilled pen (PLGB 14895/0317-18 and PLGB 14895/0320-0323), the non-clinical and clinical data are identical to those submitted previously.

In line with the legal requirements for children's medicines, the applications included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) (MHRA-100447-PIP01-22-M01). At the time of the submission of the applications the PIP was 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 01 September 2023.

II QUALITY ASPECTS

II.1 Introduction

These products consist of vials containing solution for injection.

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

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)
Water for injections

The finished products are packaged in clear glass vials with sealed stoppers, in a pack size of 1 vial.

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.

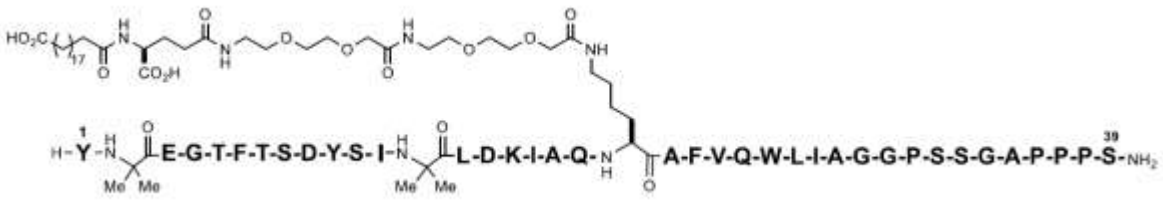
II.2 ACTIVE SUBSTANCE

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 2 years, with the following storage conditions is acceptable:

Store in a refrigerator (2 ºC – 8 ºC).
Do not freeze.
Store in original package in order to protect from light.

Mounjaro may be stored unrefrigerated for up to 21 cumulative days at a temperature not above 30 ºC and then the vial 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 prefilled 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
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 prefilled pen (PLGB 14895/0317-18 and PLGB 14895/0320-0323), the clinical data are identical to those submitted previously.

IV. 2 Pharmacokinetics
No new pharmacokinetic data have been submitted for these applications and none were required.

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

No new safety data were submitted with these applications, and none were required. The safety profile for these products is considered to be the same as Mounjaro 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg solution for injection in prefilled pen (PLGB 14895/0317-18 and PLGB 14895/0320-0323).

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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**
	Additional Risk minimisation measures: None	• 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:** None
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

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 prefilled 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.

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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**