Mounjaro®

(tirzepatide)

2.5 mg / 5 mg / 7.5 mg / 10 mg / 12.5 mg / 15 mg

solution for injection

Summary of Risk Management Plan (RMP)

Eli Lilly (Suisse) SA

Summary of the Risk Management plan (RMP) for Mounjaro (tirzépatide)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Mounjaro is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the „Arzneimittelinformation / Information sur le médicament“ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Mounjaro in Switzerland is the „Arzneimittelinformation/ Information sur le médicament“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Eli Lilly is fully responsible for the accuracy and correctness of the content of this published summary RMP of Mounjaro.

This is a summary of the RMP for Mounjaro. The RMP details important risks of Mounjaro, how these risks can be minimised, and how more information will be obtained about Mounjaro’s risks and uncertainties (missing information).

Mounjaro’s SmPC and its package leaflet give essential information to healthcare professionals and patients on how Mounjaro should be used.

This summary of the RMP for Mounjaro should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Mounjaro’s RMP.

I - The Medicine and What It is Used for

Mounjaro is authorised for T2DM (see SmPC for the full indication). It contains tirzepatide as the active substance and it is given by injection.

Further information about the evaluation of Mounjaro's benefits can be found in Mounjaro's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for CWM, including weight loss and weight maintenance, in adults with an initial BMI of

- ≥30 kg/m^2 (obesity) or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnoea, CV disease, prediabetes, or T2DM.

It contains tirzepatide as the active substance and is given by injection.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Mounjaro, together with measures to minimise such risks and the proposed studies for learning more about Mounjaro's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be

- specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- important advice on the medicine's packaging
- the authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly, and
- the medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Mounjaro is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Mounjaro are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which

there is sufficient proof of a link with the use of Mounjaro. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Medullary thyroid cancer Pancreatic malignancy Diabetic retinopathy complications
Missing information	Use in pregnancy and lactation

II.B Summary of Important Risks

Important potential risk: Medullary thyroid cancer	
Evidence for linking the risk to the medicine	In nonclinical studies, treatment-related increases in thyroid C-cell hyperplasia and neoplasia were observed with tirzepatide, at all doses, in a 2-year rat carcinogenicity study. This effect on rodent thyroids has been observed consistently with other long-acting GLP-1 RAs, including liraglutide, exenatide once weekly, dulaglutide, and semaglutide, in near-lifetime exposure carcinogenicity studies. The relevance to humans cannot be determined from clinical and nonclinical studies. At this time, there is insufficient evidence to attribute thyroid C-cell disease to tirzepatide. Given the latency for cancer, the database for tirzepatide is of insufficient size and exposure duration to assess definitively for any particular type of cancer. Nonclinical data suggest that there is a risk for MTC with tirzepatide, and this has been determined to be a key safety finding from the nonclinical development programme.
Risk factors and risk groups	Medullary thyroid carcinoma develops from the C (parafollicular) cells and accounts for 5% to 10% of all thyroid cancers (Brady 2018), and up to 25% of MTC cases develop under multiple endocrine neoplasia-2A (IARC 2018). Compared to the general population (6.6%), patients with diabetes have a higher prevalence of thyroid disorders (10.8%) (Shih et al. 2012). However, the link between T2DM and thyroid cancer is arguable. Some studies did not show an association between diabetes, including T2DM and thyroid cancer risk (Kitahara et al. 2012; Shih et al. 2012; Seo et al. 2017). Other studies showed that patients with diabetes are 20% to 34% more likely to develop thyroid cancer compared to those without diabetes (Yeo et al. 2014; Li and Qian 2017). Many studies show that the risk of thyroid cancer, specifically papillary thyroid cancer, increased in participants with overweight and obesity compared with normal-weight participants. It has been estimated that a 5-point increase in BMI and a 0.1-point increase in waist-to-hip ratio increase the risk of thyroid cancer by 30% and 14%, respectively (Schmid et al. 2015; Kitahara et al. 2020; Li et al. 2020). Although there is a positive association between obesity/overweight and papillary, follicular, and anaplastic thyroid cancers, there was an inverse association noted with MTC (Schmid et al. 2015).
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 5.3 **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • I8F-MC-B013: A Medullary Thyroid Carcinoma database linkage study See Section Post-Authorisation Development Plan of this summary for an overview of the post-authorisation development plan.
Important potential risk: Pancreatic malignancy	

Evidence for linking the risk to the medicine	There is no evidence from clinical trials that GLP-1-based therapies increase the risk of pancreatic cancer. Some literature reports indicate a causal association with these agents, while others have failed to show such an association. A joint FDA and EMA publication states that data demonstrate conflicting opinions about strength of the association (Egan et al. 2014). To date, no causal relationship between tirzepatide and pancreatic malignancy has been established. Incidence of pancreatic malignancy was similar in the tirzepatide and placebo groups in the Phase 2 and 3 clinical trials for tirzepatide.
Risk factors and risk groups	Patients with long-standing T2DM are twice more likely to have pancreatic cancer than patients without T2DM (Yadav and Lowenfels 2013). About 0.5% of patients newly diagnosed with T2DM develop pancreatic cancer within 6 years of follow-up. Obesity increases risk of pancreatic cancer, with approximate 10% or greater increases in risk of pancreatic cancer for a 5 kg/m^2 unit increase in BMI, or a 20% to 50% increased risk among those with obesity relative to participants with normal BMI (Berrington et al. 2003; Larsson et al. 2007; Renehan et al. 2008). Being the fourth leading cause of cancer mortality, pancreatic cancer is a highly mortal malignancy, with 75% of patients dying within the first year of diagnosis (Bracci 2012). The 5-year survival rate among patients with pancreatic malignancy is about 6% (Yadav and Lowenfels 2013).
Risk minimisation measures	**Routine risk minimisation measures:** • None **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • I8F-MC-B011: Tirzepatide Pancreatic Malignancy Study See Section II.C Post-Authorisation Development Plan of this summary for an overview of the post-authorisation development plan.
Important potential risk: Diabetic retinopathy complications	
Evidence for linking the risk to the medicine	Worldwide, the prevalence of DR ranges between 10% and 61% (median 28%) among patients with T2DM and between 1.5% and 31% (median 11%) among those newly diagnosed with T2DM (Ruta et al. 2013). The incidence rates of DR among adults aged 30 years and older with T2DM in the UK and Spain were 11.6 and 81.3 per 1000 people, respectively (Thomas et al. 2012; Romero-Aroca et al. 2017). Deterioration of DR among patients with improved glycaemic control is well documented with limited information for patients with T2DM specifically (Hooymans et al. 1982; Yau et al. 2012; Bain et al. 2019). A study conducted by Oslo Study Group-Brinchmann-Hansen et al. reported worsening of DR after introduction of stringent diabetes management within 3 months of treatment; approximately 50% of treated patients were affected compared with none of the patients treated conventionally (Oslo

	Study Group et al. 1985). A study conducted among patients with type 2 diabetes reported the risk of progression of DR after 3 and 9 years was 15.8% and 23%, respectively, for patients treated with intensive therapy compared with 15.3% and 27.8%, respectively, for patients undergoing treatment with either insulin or a sulphonylurea (Bain et al 2019). A meta-analysis of 4 randomised controlled trials reported that after 5 years of follow-up, more intensive glucose control was associated with a 13% reduction of eye events (risk ratio: 0.87; 95% confidence interval: 0.76, 1.00; p = 0.04; Feldman-Billard et al. 2018). Patients with a history of proliferative DR, diabetic maculopathy, or non-proliferative DR that required acute treatment were excluded from the tirzepatide clinical trial development programme. A dedicated retinopathy addendum to SURPASS-CVOT I8F-MC-GPGN (GPGN) is ongoing, which will further investigate the risk of disease progression for DR among patients treated with tirzepatide. The comparative analysis of the worsening of an existing DR with other diabetic treatment to tirzepatide treatment will be conducted after the addendum GPGN sub-study results are available. Therefore, there was limited experience to determine whether the safety profile in this patient population is different from that expected in the population without DR. In Phase 3 clinical trials, a dilated fundoscopic examination was performed when clinically indicated by any suspected adverse event of worsening retinopathy or clinically recommended during the course of the study. Worsening of fundoscopic examination result was observed in 18 tirzepatide-treated patients (0.35%).
Risk factors and risk groups	Patients with T2DM are at risk of developing microvascular complications including DR, nephropathy, and neuropathy. Modifiable risk factors for DR include high blood glucose, high blood pressure, high serum lipids, and smoking. Non-modifiable risk factors include diabetes duration, age, race, and genetic predisposition (Ding and Wong 2012; Scanlon et al. 2013).
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.4 **Additional risk minimisation measures:** • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN) See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Use in pregnant and/or breastfeeding women	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section 4.6

	• PL Section 2 **Additional risk minimisation measures:** • None

Abbreviations: DR = diabetic retinopathy; EMA = European Medicines Agency; FDA = United States Food and Drug Administration; GLP-1 = glucagon-like peptide 1; MTC: medullary thyroid cancer; PL = package leaflet; RA = receptor agonist; SmPC = Summary of Product Characteristics; T2DM = type 2 diabetes mellitus.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Mounjaro.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: A Medullary Thyroid Carcinoma Database Linkage Study (I8F-MC-B013)

Purpose of the study: This is an observational database study using a matched cohort design. This study addresses the important potential risk of MTC observed in rodents across all GLP-1 RAs.

The primary objective is 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% CIs.

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.

Study short name: Tirzepatide Pancreatic Malignancy Study (I8F-MC-B011)

Purpose of the study: This is a retrospective non-interventional cohort study that will address the safety concerns of pancreatic malignancy.

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.

Study short name: Retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN)

Purpose of the study: This is a retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN) to be performed in addition to all procedures required by Protocol I8F-MC-GPGN or any subsequent amendments to that protocol.

The study objective is

- to compare the effect of tirzepatide dose up to 15 mg QW with dulaglutide 1.5 mg QW on DR progression.
- to assess the safety of tirzepatide dose up to 15 mg QW when compared with dulaglutide 1.5 mg QW on DR.