Summary of the Risk Management Plan (RMP) V. 5.0, 20 November 2022 for

TEPMETKO®

Tepotinibum 225 mg ut Tepotinibi Hydrochloridum Monohydricum 250 mg

Film-coated Tablets

Marketing Authorization Number 68113

Marketing Authorisation Holder: Merck (Schweiz) AG, Zug

Disclaimer:
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 minimise them. The RMP summary of **Tepmetko** 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 **Tepmetko** in Switzerland is the "Arzneimittelinformation/Information sur le medicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Merck (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of **Tepmetko**.

Part VI: Summary of the Risk Management Plan

Summary of the Risk Management Plan for TEPMETKO (tepotinib)

This is a summary of the risk management plan (RMP) for TEPMETKO The RMP details important risks of TEPMETKO, how these risks can be minimized, and how more information will be obtained about TEPMETKO's risks and uncertainties (missing information).

TEPMETKO's Company Core Data Sheet (CCDS) gives essential information to healthcare professionals and patients on how TEPMETKO should be used.

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

I. The Medicine and What it is Used for

TEPMETKO is authorized for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with MET tyrosine kinase receptor exon 14 (*METex14*) skipping alterations. It contains tepotinib as the active substance and it is given by an oral route of administration.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

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

Measures to minimize 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 authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

II.A List of Important Risks and Missing Information

Important risks of TEPMETKO are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 TEPMETKO. 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	Interstitial lung disease
Important potential risks	Pleural effusion QT interval prolongation Severe hepatotoxicity
Missing information	None

II.B Summary of Important Risks

Important identified risk: Interstitial lung disease	
Evidence for linking the risk to the medicine	ILD is considered an important identified risk for tepotinib based on the frequency and the clinical course of the ILD cases in the tepotinib development program and based on the serious nature of this event. The estimated incidence of ILD-like events in VISION Cohorts A+C is 8/313 (2.6%) patients.
Risk factors and risk groups	NSCLC and advanced age are known risk factors for ILD. Other risk factors are pre-existing ILD, previous radiation of the lung, smoking, previous anticancer medicines like taxanes or any immune checkpoint inhibitor and male sex. All VISION patients with ILD-like events identified at data cutoff had at least one of these risk factors. No clear pattern emerged in VISION with regard to the risk factors, except that all patients with ILD-like events were above 60 years old, which was in accordance with the median age of 72.6 years in the overall study population. An independent panel summarized that in some cases an exacerbation of pre-existing chronic-fibrosing idiopathic interstitial pneumonia or radiation fibrosis was observed with tepotinib, which is consistent with what is described in the literature. However, as per Sponsor opinion, the number of cases with ILD is too small to draw reliable conclusions on pre-existing ILD or fibrosis as specific risk factor for tepotinib induced ILD.
Risk minimization measures	Routine risk minimization measures • *CCDS sections 4,6 and 10* • *Advice in CCDS Section 4 to withhold or discontinue tepotinib if patients develop pulmonary symptoms indicative of ILD-like reactions* • *Recommendation in CCDS Section 6 to monitor for symptoms of ILD-like reactions, to investigate, to treat patients and to permanently discontinue tepotinib if ILD is confirmed* • *Medical prescription* Additional risk minimization measures • None
Additional pharmacovigilance activities	None

CCDS=company core data sheet; ILD=interstitial lung disease

Important potential risk: Pleural effusion	
Evidence for linking the risk to the medicine	Pleural effusion was observed in the tepotinib clinical development program (incidence of 14.4% in VISION Cohorts A + C). Although there is insufficient evidence to confirm a causal association with tepotinib treatment, considering the incidence of this event in the VISION study, and the consequence of this event on the interpretation of disease progression, pleural effusion has been classified as an important potential risk.
Risk factors and risk groups	Malignant pleural effusion is a common complication of malignancies, the most common cause being lung cancers. Malignant tumors can lead to the development of pleural effusion either due to the direct or indirect spread of disease. A large SEER registry study of 57,687 patients with NSCLC showed incidence of pleural effusion of 15.9% in patients receiving any anticancer therapy. Malignant pleural effusion is the most common cause of pleural effusion in lung, breast, and gynecologic cancer. Hepatic hydrothorax is the main cause in HCC. Pleural effusions may also result from other benign conditions such as congestive heart failure, cirrhosis, or pulmonary embolism.
Risk minimization measures	Routine risk minimization measures: • *Medical prescription* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	None

HCC=hepatocellular carcinoma; NSCLC=non-small cell lung cancer

Important potential risk: QT interval prolongation	
Evidence for linking the risk to the medicine	Data on the possible effects of tepotinib exposure on the QTc interval have been analyzed from multiple sources. Non-clinical findings and exposure-QTcF analysis have not indicated a risk with tepotinib. Very few patients in the VISION study reported adverse events of QTc prolongation or single episodes of worst shift in QTcF from baseline of >60 ms with no conclusive alternative explanations for these QTc effects. All patients were asymptomatic, and the findings were nonserious, mainly non-severe, isolated, and had late and not consistent onset. The evidence is insufficient to establish a causal link. Noting the potentially serious consequences of QT prolongation the Applicant considers QT prolongation to be an important potential risk for tepotinib.
Risk factors and risk groups	Risk factors include advanced age, congenital long QT syndrome and heart disease.
Risk minimization measures	Routine risk minimization measures: • *Medical prescription* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	None

Important potential risk: Severe hepatotoxicity	
Evidence for linking the risk to the medicine	Based on the repeat-dose toxicity studies in animals, the liver/hepatobiliary system was identified as target organ of toxicity.

Important potential risk: Severe hepatotoxicity	
	Overall, hepatotoxicity observed with tepotinib is reflected by asymptomatic, nonserious, and non-severe elevation of the transaminases with no impact on-treatment or benefit-risk balance. Few patients had severe hepatotoxicity reflected by very large increases in transaminases level or by meeting Hy's law criteria. Most patients who met biological criteria of drug-induced liver injury (DILI) came from the POOL and had an alternative explanation or were confounded by underlying hepatocellular carcinoma and additionally some patients had cirrhosis. One patient from the VISION study presented with a picture of acute hepatitis followed by liver failure which resulted in a fatal outcome. However, lack of relevant follow-up information has not allowed a meaningful causality assessment of this case and to rule out a possible causal association. The Company´s position is that there is not enough evidence that tepotinib causes severe liver injury/hepatotoxicity, but adverse events suggestive of DILI including hepatic / liver failure and hepatitis (non-infectious) are being closely monitored. In this regard severe hepatotoxicity has been classified as an important potential risk in the RMP.
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization activities recommending specific clinical measures to address the risk: • *Advice to modify dose if patients develop grade 3 events or higher in CCDS Section 4.* • *Recommendation to monitor for liver function (ALT, AST and bilirubin) before and during treatment in CCDS Section 6.* • *Medical prescription* Additional risk minimization measures: • *None*
Additional pharmacovigilance activities	None.

CCDS=company core data sheet; DILI=drug-induced liver injury; RMP=risk management plan; ALT=alanine transaminase; AST=aspartate aminotransferase.

II.C Post-authorization Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of TEPMETKO.

II.C.2 Other Studies in the Post-Authorization Development Plan

There are no studies required for TEPMETKO.