Summary of the Risk Management Plan (RMP) V. 1.0, January 2020 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**.

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 minimised, 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 authorised 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 Minimise or Further Characterise the Risks

Important risks of Tepmetko, together with measures to minimise such risks and the proposed studies for learning more about Tepmetko'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;
- 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 (PSUR) 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 minimise 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 (ILD)
Important potential risks	Pleural effusion QT interval prolongation
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. Taking into account information received after the DCO, 7 cases (3.9%) of ILD-like adverse reactions have been reported in patients with NSCLC treated with tepotinib 500 mg once daily in the VISION study (Cohort A + C).
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, and previous cancer medicines like taxanes or any immune checkpoint inhibitor and male sex. All VISION patients with ILD-like events identified at DCO 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 to the median age of 72.6 years in the overall study population.
Risk minimisation measures	Routine risk minimisation measures • *CCDS sections 4,6 and 10*

Important identified risk: Interstitial lung disease	
	• *Advice in CCDS section 4 to withhold or discontinue tepotinib if patients develop ILD-like reactions* • *Recommendation in CCDS section 6 to monitor for symptoms of ILD-like reactions, to investigate, to treat patients and to discontinue tepotinib if ILD is confirmed* • *Medical prescription* Additional risk minimisation measures • None

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 13.8% 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 anti-cancer 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 minimisation measures	Routine risk minimization measures: • *Medical prescription* Additional risk minimization measures: • *None*

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 and exposure QTcF analysis have not indicated a risk with tepotinib. In an exposure-QTc analysis, the QTcF interval prolongation potential of tepotinib was assessed in 285 patients with various solid tumours following single or multiple daily doses of tepotinib ranging from 27 mg to 1,261 mg. Tepotinib did not prolong the QTcF interval to a clinically relevant extent. However, there are 3 reported AEs from VISION cohorts A + C which describe multiple episodes of QTc prolongation occurring on-treatment and without conclusive alternative explanations for these QTc effects. In addition, 3 patients who experienced a worst shift in QTcF from baseline of >60 ms, did not involve notable alternative explanations for QT prolongation other than mild electrolyte abnormalities which may not be sufficient to account for these QTc findings. Noting the potentially serious consequences of QT prolongation and the increased susceptibility of patients with cancer to this condition, the QT prolongation is considered 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 minimisation measures	Routine risk minimization measures: • *CCDS Section 14* • *Medical prescription* Additional risk minimization measures: • *None*

II.C Post-authorisation Development Plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Tepmetko.

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

There are no studies required for Tepmetko.