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 summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how TEPMETKO should be used.

This summary of the RMP for TEPMETKO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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 as monotherapy is authorised for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (*METex14*) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy. It contains tepotinib as the active substance and it is given by an oral route of administration.

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

https://www.ema.europa.eu/en/medicines/human/EPAR/tepmetko

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 minimization 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.*

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) QT interval prolongation Severe oedema
Important potential risks	Pleural effusion 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 ILD incidence in VISION Cohorts A+C is 8/291 (2.7%) 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, 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 with the median age of 72.0 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 • *SmPC Sections 4.2,4.4, and 4.8* • *Advice in SmPC Section 4.2 to withhold or discontinue tepotinib if patients develop ILD-like reactions* • *Recommendation in SmPC Section 4.4 to monitor for symptoms of ILD-like reactions, to investigate, to treat patients and to discontinue tepotinib if ILD is confirmed*

Important identified risk: Interstitial lung disease	
	• *Package leaflet Sections 2 and 4* • *Medical prescription* Additional risk minimization measures • *None*
Additional pharmacovigilance activities	None

Important identified 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 analysed from multiple sources. Non-clinical findings and exposure-QTcF analysis have not indicated a risk for clinically relevant effects on the QTc interval at the recommended dose of tepotinib. At the recommended dose of 500 mg QD, no large mean increases in QTc (i.e., > 20 ms) were detected in patients with various solid tumour. 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 non-serious, mainly non-severe, isolated and had late onset. 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: • SmPC Sections 4.4 and 4.8 • Recommendation for monitoring (e.g., ECG, electrolytes) in patients at risk of developing QTc prolongation in SmPC Section 4.4. • Package leaflet Sections 2 and 4 • Medical prescription Additional risk minimization measures: *None*
Additional pharmacovigilance activities	None

Important identified risk: Severe oedema	
Evidence for linking the risk to the medicine	As severe and serious events of oedema have been observed with tepotinib, severe oedema has been classified as an Important identified risk in the RMP in order to further characterize these events.
Risk factors and risk groups	Unknown
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 • Advice to reduce the dose, interrupt or discontinue tepotinib treatment if patients develop grade 3 events or higher in SmPC Section 4.2. Package leaflet Section 4 • Medical prescription Additional risk minimization measures: *None*
Additional pharmacovigilance activities	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 13.1% 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 tumours 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 gynaecologic 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

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. Overall, hepatotoxicity observed with tepotinib is reflected by asymptomatic, non-serious 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 drug-induced liver injury 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 measures • *SmPC Sections 4.2, 4.4 and 4.8* • *Recommendation in SmPC Section 4.4 to monitor for liver enzymes (ALT and AST), and bilirubin before and during treatment.* • *Advice in SmPC Section 4.2 to reduce the dose, interrupt or discontinue tepotinib treatment if patients develop grade 3 events or higher (ALT and/or AST greater than 5 times upper limit of normal).* • *Package leaflet Sections 2 and 4* • *Medical prescription* Additional risk minimization measures: *None*
Additional pharmacovigilance activities	None

II.C Post-authorisation Development Plan

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

There are no other studies which are conditions of the marketing authorisation.

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

There are no other studies required for TEPMETKO.