

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214096Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214096
PDUFA Goal Date	February 28, 2021
OSE RCM #	2020-1102 and 1106
Reviewer Name	Mei-Yean Chen, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Division Deputy Director (Acting)	Doris Auth, Pharm.D.
Review Completion Date	December 3, 2020
Subject	Evaluation of Need for a REMS
Established Name	Tepotinib
Trade Name	Tepmetko
Name of Applicant	EMD Serono, Inc.
Therapeutic Class	a kinase inhibitor
Formulation(s)	225 mg oral tablet
Dosing Regimen	450 mg orally once daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity tepotinib is necessary to ensure the benefits outweigh its risks. EMD Serono, Inc. submitted a New Drug Application (NDA) 214096 for tepotinib with the proposed indication for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations. This indication is proposed to be approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. The risks associated with tepotinib include interstitial lung disease (ILD)/Pneumonitis, hepatotoxicity, and Embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRM) and Division of Oncology 2 (DO2) have agreed that a REMS is not needed to ensure the benefits of tepotinib outweigh its risks. Metastatic NSCLC is a serious and life-threatening disease, and there is an unmet medical need for additional effective therapies for patients. The clinical trial of tepotinib demonstrated a clinically meaningful overall response rate. The review division believes this is appropriate for accelerated approval. The risks of interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, and embryo-fetal toxicity associated with tepotinib will be described in Warnings and Precautions of the labeling. At the time of this review, none of these risks warrants a boxed warning. The clinicians, typically oncologists, who will prescribe tepotinib are familiar by their experience and training with the management of these toxicities without additional risk mitigation measures beyond labeling.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)^a tepotinib is necessary to ensure the benefits outweigh its risks. EMD Serono, Inc. submitted a New Drug Application (NDA) 214096 for tepotinib with the proposed indication for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations. This indication is proposed to be approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. This application is under review in the Division of Oncology 2 (DO2). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Tepotinib is a kinase inhibitor that targets MET, including the mutated variant produced by MET exon 14 skipping. Tepotinib blocks MET phosphorylation and showed antitumor activity in multiple tumor

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

models derived from diverse cancer types. The antitumor activity of tepotinib was especially pronounced in tumors with oncogenic alterations of MET, such as METex14 skipping alterations.

Tepotinib will be supplied as 225 mg oral tablet. The recommended dose of tepotinib is 450 mg (two tablets) orally once daily until disease progression or unacceptable toxicity.^b Tepotinib was recently approved in Japan in (March 2020) for the treatment of patients with unresectable, advanced, or recurrent NSCLC with MET ex14 skipping alterations.¹

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 214096 relevant to this review:

- 02/11/2016: Investigation New Drug (IND) 128073 for NSCLC was submitted.
- 09/10/2019: Breakthrough therapy designation granted.
- 06/29/2020: Complete NDA submitted.
- 10/01/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tepotinib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Lung cancer is the leading cause of cancer death in men and the second leading cause of cancer death in women globally, with estimated 2.1 million new cases and 1.8 million deaths worldwide for 2018. In the United States (US) in 2020, there were about 228,000 new cases of lung cancer and more than 135,000 deaths from lung cancer.^{c2} NSCLC accounts for 85% of globally diagnosed lung cancer cases. Most newly diagnosed NSCLC patients have advanced disease. If not treated, NSCLC is fatal in most patients within one year or less.^d

Alterations of the MET signaling pathway are found in various cancer types, including 3% to 4% of NSCLC cases, and correlate with aggressive tumor behavior and poor clinical prognosis. Patients with METex14 skipping alterations are usually older than those with NSCLC harboring other alterations. They are facing poor clinical prognosis and in need of new therapeutic options.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

NSCLC treatment options include surgery, radiation, and chemotherapy. The usual chemotherapy includes cisplatin or carboplatin plus docetaxel, gemcitabine, paclitaxel, vinorelbine, or pemetrexed. A

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (D): *The expected or actual duration of treatment with the drug.*

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

targeted drug alone or in combination with chemotherapy may treat patients whose cancer contains certain molecular biomarkers. Targeted therapies include erlotinib, afatinib, gefitinib, bevacizumab, crizotinib, and ceritinib. Second-line therapy includes atezolizumab, pembrolizumab, nivolumab, and ramucirumab.³

METex14 skipping alterations in NSCLC give rise to an aberrant signaling receptor that is targetable with selective MET inhibitors. On 05/06/2020, capmatinib,⁴ a MET inhibitor, received accelerated approval by the Agency for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to METex14 skipping as detected by an FDA-approved test. Capmatinib carries risks of ILD/pneumonitis, hepatotoxicity, photosensitivity, and embryo-fetal toxicity that are described in Warnings & Precautions in the labeling. There is no boxed warning for capmatinib.

4 Benefit Assessment

A single-arm, open-label, multicenter nonrandomized, multicohort study (VISION, NCT02864992) in adult patients with locally advanced or metastatic NSCLC harboring MET ex14 skipping alterations was used to evaluate the efficacy of tepotinib. MET ex14 skipping alterations was prospectively tested by next-generation sequencing in tissue (RNA-based) or plasma (ctDNA-based) clinical trial assays. Patients received tepotinib 450 mg once daily until disease progression or unacceptable toxicity. The major efficacy outcome measure was confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by a Blinded Independent Review Committee (BIRC). Duration of response (DOR) by BIRC is the additional efficacy outcome measure.⁵

In the VISION trial, the efficacy population included 69 treatment naïve patients and 83 previously treated patients. The median age was 73 years (range 41 to 94 years), 48% female, 71% White, 25% Asian. Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 27% of patients and PS was 1 in 73% of patients, 43% never smoked, and 98% had metastatic disease. Table 1 below demonstrates efficacy results in the VISION study.

Table 1 Efficacy results in the VISION study

Efficacy parameter	Treatment naïve, n=69	Previously treated, n=83
Overall response rate, %	45	45
(95% confidence interval)	(33, 57)	(34, 56)
Median duration of response (DOR), months	10.8	11.1
(95% confidence interval)	(6.9, not estimable)	(9.5,18.5)
Patients with DOR ≥ 6 months, %	68	76

5 Risk Assessment & Safe-Use Conditions

The safety of tepotinib was evaluated in a pooled safety population (373 patients) that includes patients enrolled in five open-label, single-arm studies receiving tepotinib as single agent at a dose of 450 mg once daily. This included 181 patients with NSCLC positive for METex14 skipping alterations.

All risks^e associated with tepotinib listed below are currently included in the draft labeling⁵ Section 5 Warnings and Precautions.

5.1 INTERSTITIAL LUNG DISEASE/PNEUMONITIS

Interstitial lung disease (ILD)/pneumonitis, which can be fatal, was reported in patients treated with tepotinib in the VISION study. In the VISION study, ILD/pneumonitis occurred in 1.8% of patients, with one patient experiencing a grade ≥ 3 on day 21; this event resulted in death.

If approved, healthcare providers (HCPs) will be advised to monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. The product information will also advise HCPs to withhold tepotinib immediately in patients with suspected ILD/pneumonitis and discontinue tepotinib permanently if no other potential causes of ILD/pneumonitis are identified.

5.2 HEPATOTOXICITY

Increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) occurred in 16% of patients treated with tepotinib in the VISION study. Grade 3 or 4 elevated ALT/AST occurred in 4.7% of patients.. Three patients discontinued tepotinib due to increased ALT/AST and one patient died due to hepatic failure .

HCPs will be advised to monitor liver function tests prior to the initiation of tepotinib, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated. HCPs will be also advised to withhold, reduce the dose, or permanently discontinue tepotinib based on severity of the hepatotoxicity.

5.3 EMBRYO-FETAL TOXICITY

Tepotinib can cause fetal harm when administered to a pregnant woman, based on findings from nonclinical studies and its mechanism of action. Oral administration of tepotinib to pregnant rabbits during the period of organogenesis resulted in malformations (teratogenicity) and anomalies at exposures less than the human exposure based on area under the curve (AUC) at the recommended 450 mg daily dose.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

The draft label states to advise pregnant women of the potential risk to a fetus. The draft label also recommends advising females of reproductive potential or males with female partners of reproductive potential to use effective contraception during therapy and for at least one week after the last dose.

6 Expected Postmarket Use

If approved, it is expected that oncologists will be the likely health care providers to prescribe tepotinib, in both inpatient and outpatient settings.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tepotinib beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of tepotinib on the basis of the efficacy and safety information currently available. The clinical reviewer's preliminary findings are that the application is appropriate for accelerated approval and the risks of ILD/pneumonitis, hepatotoxicity, and embryo-fetal toxicity will be communicated in Warnings and Precautions. The clinical reviewers believe that these risks are manageable with dose interruption and the events can be appropriately handled with labeling alone.

This reviewer recommends that, if tepotinib is approved, a REMS is not necessary to ensure its benefits outweigh its risks. ILD/pneumonitis, hepatotoxicity, and embryo-fetal toxicity will be adequately described in the labeling. At the time of this review, none of these risks warrants a boxed warning. The clinicians, typically oncologists, who will prescribe tepotinib are familiar by their experience and trainings in the management of these toxicities without additional risk mitigation measures beyond labeling.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, DRM and DO2 agree that a REMS is not necessary for tepotinib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

¹ EMD Serono Inc. Application Orientation Meeting of tepotinib NDA 214096, 07/13/2020

² American Cancer Society. Key statistics for Lung Cancer. www.cancer.org/cancer/lung-cancer/about/key-statistics.html. Accessed 07/01/2020

³ <https://www.lungcancer.org/find-information/publications/163-lung-cancer-101/269-non-small-cell-lung-cancer-treatment>, accessed 09/21/2020

⁴ Capmatinib prescribing information <https://www.hcp.novartis.com/products/tabrecta/met-exon-14-skipping-mutation-nsclc/>, accessed 09/21/2020

⁵ Tepotinib draft prescribing information, accessed 11/25/2020

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