



NDA 214096

**ACCELERATED APPROVAL**

EMD Serono Inc.  
Attention: Virginia Vetter, M.S., RAC  
Director, Global Regulatory Affairs, Immuno-Oncology  
45A Middlesex Turnpike  
Billerica, MA 01821

Dear Ms. Vetter:

Please refer to your new drug application (NDA) dated June 29, 2020, received June 29, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tepmetko (tepotinib) tablets.

This new drug application provides for the use of Tepmetko (tepotinib) tablets for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (*MET*) exon 14 skipping alterations.

**APPROVAL & LABELING**

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.<sup>2</sup>

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND CONTAINER LABELING**

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, submitted on October 19, 2020 for the blister package, and on November 30, 2020 for the carton packages, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 214096.**” Approval of this submission by FDA is not required before the labeling is used.

### **DATING PERIOD**

Based on the stability data submitted to date, the expiry dating period for Tepmetko (tepotinib) tablets shall be 30 months from the date of manufacture when stored at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Tepmetko (tepotinib) tablets should be stored in their original package in order to protect from moisture.

### **ADVISORY COMMITTEE**

Your application for Tepmetko was not referred to an FDA advisory committee because this drug is not the first in its class.

### **ACCELERATED APPROVAL REQUIREMENTS**

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated January 27, 2021. This requirement, along with required completion dates, is listed below.

4013-1      Submit the final reports including datasets from clinical studies to confirm and further characterize the clinical benefit of tepotinib for the treatment of patients with non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping alterations who are treatment-naïve and who have previously received systemic therapy, by providing a more precise estimation of the blinded independent central review-assessed overall response rate and duration of response. This report will contain data from patients with

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NSCLC harboring MET exon 14 skipping alterations; data from at least 130 patients who are treatment naïve, after all responders have been followed for at least 12 months from the date of initial response (or until disease progression, whichever comes first); and from at least 143 patients who have been previously treated with systemic therapy, after all responders have been followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first).

Final Report Submission: 04/2023

Submit clinical protocols to your IND 128073 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart H Postmarketing Requirement(s).**”

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of increased drug exposure when tepotinib is administered concomitantly with strong CYP3A4 and P-gp inhibitors.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

- 4013-2      Conduct a drug interaction study to evaluate the effect of itraconazole on the single dose pharmacokinetics of tepotinib to assess the magnitude of increased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 and P-gp inhibitors. Design and conduct the study in accordance with the FDA Guidance for Industry titled “[Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.](#)”

The timetable you submitted on January 27, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2021
Final Protocol Submission:	09/2021
Study Completion:	03/2022
Final Report Submission:	09/2022

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.<sup>3</sup>

Submit clinical protocol(s) to your IND 128073 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

**Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

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<sup>3</sup> See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 4013-3      Conduct a drug interaction study to evaluate the effect of rifampin on the single dose pharmacokinetics of tepotinib to assess the magnitude of decreased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 inducer and moderate CYP2C8 inducer. Design and conduct the trial in accordance with the FDA Guidance for Industry titled "[Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.](#)"

The timetable you submitted on January 27, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2021
Trial Completion:	01/2022
Final Report Submission:	07/2022

- 4013-4      Submit a summary of the final report of an analytical and clinical validation study, using clinical trial data, that is adequate to support labeling of an in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of tepotinib for patients diagnosed with non-small cell lung cancer, whose tumors harbor MET exon 14 skipping. The results of the validation study may inform product labeling.

The timetable you submitted on January 27, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission:	01/2022
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A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 128073 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

### **PROMOTIONAL MATERIALS**

Under 21 CFR 314.55, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.55, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.<sup>4</sup>

### **REPORTING REQUIREMENTS**

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

### **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the

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<sup>4</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Stacie Woods, Pharm.D., Regulatory Health Project Manager, at 301-796-4803.

Sincerely,

*{See appended electronic signature page}*

Julia Beaver, M.D.  
Deputy Director (acting), Office of Oncologic  
Diseases  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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JULIA A BEAVER  
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