

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214096Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 8, 2020

To: Stacie Woods, Regulatory Project Manager
Division of Oncology 2 (DO2)

William Pierce, PharmD, Associate Director for Labeling
Office of Oncologic Diseases

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: Follow-up to OPDP Labeling Comments for TEPMETKO® (tepotinib) tablets, for oral use

NDA: 214096

We refer to our November 25, 2020 review of the draft blister label for Tepmetko (attached) submitted by the Applicant to the electronic document room on October 19, 2020, and our associated comment. We further refer to the Applicant's response to our comment in their November 30, 2020 submission (eCTD sequence #40, SD-40). In light of the Applicant's November 30, 2020, response, OPDP has no comments on the attached draft blister label submitted by the Applicant on October 19, 2020.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer, PharmD at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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LYNN M PANHOLZER
12/08/2020 10:10:29 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: November 25, 2020

To: Stacie Woods, Regulatory Project Manager
Division of Oncology 2 (DO2)

William Pierce, PharmD, Associate Director for Labeling
Office of Oncologic Diseases

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for TEPMETKO® (tepotinib) tablets, for oral use

NDA: 214096

In response to DO2's consult request dated June 29, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for TEPMETKO® (tepotinib) tablets, for oral use.

Labeling: OPDP's comments on the proposed PI are based on the draft PI obtained from Sharepoint on November 24, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the proposed PPI was completed, and comments on the proposed PPI were sent under separate cover on November 23, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labels submitted by the Applicant to the electronic document room on October 19, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer, PharmD at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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LYNN M PANHOLZER
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 23, 2020

To: Stacie Wood, PharmD
Regulatory Project Manager
Division of Oncology II (DO2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Lynn Panholzer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TEPMETKO (tepotinib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 214096

Applicant: EMD Serono, Inc.

1 INTRODUCTION

On June 29, 2020, EMD Serono, Inc., submitted for the Agency's review the final submission for a Real-Time Oncology Review to complete their original New Drug Application (NDA) 214096 for TEPMETKO (tepotinib) tablets, for oral use. The proposed indication is for the treatment of patients with advanced non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on June 29, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TEPMETKO (tepotinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TEPMETKO (tepotinib) tablets PPI received on June 29, 2020, and received by DMPP and OPDP on November 17, 2020.
- Draft TEPMETKO (tepotinib) tablets Prescribing Information (PI) received on June 29, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 17, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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BARBARA A FULLER
11/23/2020 12:53:50 PM

LASHAWN M GRIFFITHS
11/23/2020 01:07:55 PM

Clinical Inspection Summary

Date	11/10/2020
From	Michele Fedowitz, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Luckson, Mathieu M.D. Erin Larkins, M.D. Harpreet Singh, M.D. Division of Oncology (DO2) Office of Oncologic Diseases (OOD)
NDA #	214096
Applicant	EMD Serono Inc.
Drug	Tepotinib
NME (Yes/No)	Yes
Therapeutic Classification	Tyrosine kinase inhibitor
Proposed Indication	Advanced non-small cell lung cancer (NSCLC) with MET exon 14 (METex14) skipping alterations
Consultation Request Date	June 26, 2020
Summary Goal Date	November 15, 2020
Action Goal Date	December 11, 2020
PDUFA Date	February 28, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from a single study (Study MS200095-0022) were submitted to the Agency in support of a New Drug Application (NDA 214096) for tepotinib for the above proposed indication. Two clinical investigators, Drs. Paul Paik (Site 104) and Xiuning Le (Site 152) were selected for clinical inspections, as well as the central imaging contract research organization. (b) (4)

A few data discrepancies regarding the independent radiology endpoint results were identified at the inspection of (b) (4). These discrepancies were subsequently corrected by the Sponsor, as detailed below in Section III. The inspections otherwise revealed no significant findings at the audited clinical investigator sites or the imaging CRO site. There was no evidence of underreporting of serious adverse events or significant protocol deviations. Based on the results of these inspections, the study appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO appear to be acceptable in support of the NDA.

II. BACKGROUND

EMD Serono Inc. seeks approval of tepotinib for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with MET exon 14 (METex14) skipping alterations. In support of the NDA, the Applicant submitted clinical data from Study MS200095-0022 (NCT02864992), titled “A Phase II single-arm trial to investigate tepotinib in advanced (locally advanced or metastatic) non-small cell lung cancer with *MET* exon 14 (*MET*ex14) skipping alterations or *MET* amplification.”

Study MS200095-0022 is an ongoing Phase 2, single-arm, open-label study in subjects with *MET* altered NSCLC. Initially, subjects were enrolled into 2 cohorts:

- **Cohort A:** Subjects tested positive for *MET*ex14 skipping alterations, regardless of *MET* amplification status
- **Cohort B:** Subjects tested positive for *MET* amplification in liquid biopsy (LBx) and negative for *MET*ex14 skipping alterations

Starting with protocol version 6, instituted March 26, 2019, Cohort C was added, as a confirmatory study:

- **Cohort C:** Subjects tested positive for *MET*ex14 skipping alterations, regardless of *MET* amplification status

At the time of submission, the efficacy analysis set consisted of cohort A overall and a subset of cohort A who received a first dose of the study drug prior to 4/2/2019; and the safety analysis set consisted of cohorts A + C.

Subjects with NSCLC signed a prescreening informed consent for evaluation of *MET* alteration status. Subjects who were positive for *MET* alteration signed an additional written informed consent prior to additional screening procedures. If eligibility criteria were met, subjects were enrolled into the appropriate cohort. All enrolled subjects received 500 milligrams (mg) of tepotinib once daily in continuous cycles of 21-day duration until disease progression, death, adverse event (AE) leading to discontinuation or withdrawal of consent.

The primary objective is to assess the efficacy of tepotinib in subjects with advanced (locally advanced or metastatic) NSCLC. The primary endpoint is objective response determined according to RECIST Version 1.1, based on independent review. Objective response is defined as either a confirmed complete response (CR) or partial response (PR) from first administration of trial treatment to first observation of progressive disease (PD). The key secondary endpoint was objective response determined according to RECIST Version 1.1, based on investigator review.

Subjects had tumor assessments according to RECIST V1.1 in the screening period and then every 6 weeks following the Cycle 1, Day 1 visit until 9 months, then every 12 weeks thereafter until disease progression, death or withdrawal of consent. An End of Treatment visit occurred within 14 days of last dose of trial treatment and a 30-day follow-up visit was to be performed after the last dose of trial treatment for all subjects who discontinued trial treatment

permanently, including subjects who completed an End of Treatment visit.

The study was conducted at 128 study centers in Belgium, France, Germany, Israel, Italy, Japan, Poland, South Korea, Spain, Taiwan, The Netherlands, and the USA (27 study centers in the USA and 22.7% of the subjects were enrolled in study centers in the US). The study enrolled the first subject on September 6, 2016 and the data cutoff for the current report was January 01, 2020. The study is ongoing. At the time of data cutoff, 152 subjects were enrolled and treated in the efficacy analysis set: cohort A overall, and 99 subjects in the subset of cohort A who received a first dose of the study drug prior to 4/2/2019. This does not include Subject (b) (6) who was not included in the intent to treat population because of a protocol violation. The safety analysis set, consisting of cohorts A + C, included 181 subjects.

The Review Division (DO3) and OSI selected two participating clinical investigators for inspections using risk-based approach including high enrollment and efficacy results: Drs. Enriqueta Felip Font (Site 601) and Paul Paik (Site 104). The scheduled inspection of Dr. Font in Spain was cancelled because of the COVID-19 pandemic. At the time, Spain had restricted entry into the country which prevented ORA from travelling to the site. The General Data Protection Regulation (GDPR) restrictions in the European Union (EU) prevented the conduct of a remote regulatory assessment of the site. In collaboration with DO3, the clinical investigator Dr Xiuming Le (Site 152) was selected to replace the requested inspection of Dr. Font.

III. RESULTS

1. Dr. Paul Paik (CI Site 104)

Memorial Sloan Kettering Cancer center
Rockefeller Outpatient Pavilion
160 East 53rd Street
New York, New York 10022
Inspection dates: September 9-11 and 15-17, 2020

This investigator was inspected as a surveillance inspection for Study MS200095-0022. This was the first FDA inspection for this investigator.

The enrollment logs inspected at the site were consistent with the data listings. At the time of data cut off, the investigator site had screened 22 subjects and enrolled 14, all in cohort A, with a subset of 9 subjects enrolled at the site prior to April 2, 2019. Of these 9 subjects, one remained on treatment at the time of data cutoff (Subject (b) (6)), five had discontinued secondary to disease progression (Subjects (b) (6)), 2 had discontinued secondary to adverse events (Subjects (b) (6) and 1 had died (Subject (b) (6)). Of the 5 subjects enrolled after April 2, 2019 into cohort A: 4 were still on treatment at the time of data cutoff (Subjects (b) (6)) and one was off treatment due to disease progression (Subject (b) (6)).

The inspection reviewed the subject records for all 9 subjects enrolled before April 2, 2019 and compared them to the data listings. The reviewed records included eligibility criteria, informed consent (pre-screening and main), CT reports, progress notes, adverse events, ECGs, lab results (including pharmacokinetic worksheets), vital signs, drug return forms and patient pill diaries. The additional 5 subjects enrolled after April 2, 2019 were reviewed for informed consent.

The inspection also reviewed study records including Form FDA 1572s, financial disclosures, task delegation logs, monitoring logs, IRB communications, Clinical Research toxicity Log (adverse events), drug accountability and shipping records.

The primary endpoint was based on independent review of imaging. The image capture and transfer records at the site were reviewed. All imaging studies were confirmed to have been correctly sent to the CRO responsible for the independent review of imaging (b)(4). The key secondary endpoint, objective response determined according to RECIST Version 1.1 based on Investigator review, was verified with source data (CT reports and RECIST 1.1 assessment documents).

The ECG source data could not be verified with the data listings because the data listings reflected the central ECG reads (as per protocol) which were not available at the site.

No significant data discrepancies were identified between source records at the site and the submitted data listings. Specifically, there was no under-reporting of adverse events or protocol deviations. The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Paik at the conclusion of the inspection.

2. Dr. Xiuning Le (CI Site 152)

University of Texas MD Anderson Cancer Center
Unit 432 Thoracic Head and Neck Medical Oncology
1400 Holcombe Boulevard
Houston, Texas
USA 77030
Inspection dates: September 9-11, 2020

This investigator was inspected as a surveillance inspection for Study MS200095-0022. This was the first FDA inspection for this investigator.

At the time of the inspection, the investigator had screened 29 subjects and enrolled 12 subjects into the study. Two of the enrolled subjects at the site are in the efficacy analysis population for the submission, and both have discontinued study treatment: Subject (b)(6) discontinued due to disease progression and Subject (b)(6) discontinued due to adverse events. In addition to Subjects (b)(6) 7 additional enrolled subjects at the site are in the safety analysis population for the submission (Subjects (b)(6) in Cohort A and Subjects (b)(6) in Cohort C). Three subjects enrolled at the site were enrolled into Cohort B (Subjects (b)(6)); these subjects are not included in the current efficacy population.

The inspection reviewed the source records for all 12 subjects and compared them to the data listings. The reviewed records included eligibility criteria, informed consent documents, medical records in the EHR including labs, vitals, demographics, imaging, pathology reports, and ECGs. Additional study records reviewed included monitoring records, drug accountability and shipping records, and logs, including: training, task delegation, AEs, SAEs, and protocol deviation logs.

The image capture and transfer records at the site were reviewed for all study-related imaging. All imaging studies were confirmed to have been sent to the CRO responsible for the independent review of imaging (b) (4) per the protocol. The key secondary endpoint, objective response by investigator assessment was verified against source data. No significant data discrepancies were identified. There was no under-reporting of adverse events or protocol deviations. The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Le at the conclusion of the inspection.

3. (b) (4) (Imaging CRO)

Inspection Dates: August 3-5, 2020

This CRO was inspected as a data audit and surveillance inspection for Study MS200095-0022. This CRO has been inspected previously on 7/15/2019, 3/22/2018, and 6/23/2016, all classified as NAI.

(b) (4) was contracted to conduct the independent radiology review for this study. They conducted reviews for timepoint response assessments but did not determine the primary endpoint objective response. The inspection reviewed 153 Cohort A subject records including radiology results and source documents and compared them to the data listings. Additionally, the inspection reviewed documents related to the conduct of the study, including the organizational charts, contracts, and charters.

All overall response data up to data cutoff (January 1, 2020) in the data listings were compared to the results available at the site.

There were 3 subjects who had an incorrect response assessment in the data listings due to a protocol deviation whereby source data (cytology reports) were sent to (b) (4) after the data cutoff. This deviation is described on pages 102-103 (section 10.2) in the CSR. From the initiation of the study in September 2016 through November 2018, cytology results were collected and sent (b) (4) for inclusion in the radiology review, as specified in the protocol. The process was interrupted from November 13, 2018 until December 12, 2019, when the issue was identified by the sponsor. The missing cytology reports were subsequently sent, however, this occurred after the January 1, 2020 data cutoff and the delayed cytology results were not incorporated into the endpoint evaluations. A total of 11 subjects were affected. The inspection revealed that this deviation affected the response assessments for 3 of the 11 subjects.

Specifically, the Overall Response changed based on cytology that was sent to (b) (4) AFTER the data cutoff, as follows:

Table 1: Overall response data discrepancies related to delayed cytology results

Subject #	Date	Data Listing Overall Response	Changes to the Response Determinations Due to Cytology Results
(b) (6)	(b) (6)	PD	PR*
(b) (6)	(b) (6)	PD	PR*
(b) (6)	(b) (6)	PD	PR*
(b) (6)	(b) (6)	PD	PR*
(b) (6)	(b) (6)	SD	PD^
(b) (6)	(b) (6)	SD	PD^
(b) (6)	(b) (6)	SD	PD^
(b) (6)	(b) (6)	SD	PD^
(b) (6)	(b) (6)	PR	PD^

*Reason for Changes: Biopsy/Cytology Report was Negative for cancer

^Reason for changes: Cytology report was Positive for cancer

Reviewer's comments: The data discrepancies were discussed with the review division on October 13, 2020. The sponsor corrected the discrepancies and submitted updated data within the September 3, 2020 submission (with a July 1, 2020 data cutoff.) The changes in response based on the corrected data improved the outcome of the drug for subject (b) (6) and worsened the outcome for subjects (b) (6)

Two response assessments were missing in the data listings for Subject (b) (6) specifically, the visit 15 (b) (6) and visit 16 (b) (6) imaging dates. This was due to a problem with the data export application (b) (6). The error was discovered (b) (4) and the new data was sent to the sponsor on 7/30/2020. The following is an excerpt from the data listings:

Table 2: Subject (b) (6) Target Lesion Response per IERC and Investigator

Evaluation Visit	Date	IERC Response	Investigator Response
Unscheduled	(b) (6)	SD	PR
Visit 1	(b) (6)	SD	PR
Visit 2	(b) (6)	SD	PR
Visit 3	(b) (6)	PR	PR
Visit 4	(b) (6)	PR	PR
Visit 5	(b) (6)	PR	PR
Visit 6	(b) (6)	PR	PR
Visit 7	(b) (6)	PR	CR
Visit 8	(b) (6)	PR	CR
Visit 9	(b) (6)	PR	CR
Visit 10	(b) (6)	PR	CR
Visit 11	(b) (6)	PR	CR
Visit 12	(b) (6)	PR	CR
Visit 13	(b) (6)	PR	CR
Visit 14	(b) (6)	PR	CR
Visit 15	(b) (6)	*	CR
Visit 16	(b) (6)	*	CR

*Central response assessment missing and sent to was sent (b) (4) to the Sponsor on 7/30/2020

Reviewer's Comments: This data discrepancy in the single subject described above is unlikely to have an impact on the primary endpoint, objective response, as the subject had already achieved PR by central assessments from Visit 3 [REDACTED] (b) (6) through Visit 14 [REDACTED] (b) (6). The discrepancy does impact duration of response for this subject, a secondary endpoint.

There were no additional data discrepancies identified for the primary endpoint assessments. Blinding procedures were followed, and the inspection found no instances of unblinding. There were no regulatory findings at the site.

4. Dr. Enriqueta Felip Font (CI Site 601)

Hospital Universitari Vall d'Hebron
Oncology Department.
Passeig Vall d'Hebron, 119-129
Oncologia
Edificio Modulares Azul

The inspection of Dr. Font was canceled due to COVID-19 related travel restrictions in Spain that prevented ORA inspectors from traveling to the site. The GDPR restrictions in the EU prevented the conduct of a remote regulatory assessment of the site. Following discussions between OSI and DO2, a decision was made to inspect Dr. Xiuning Le to replace this site.

{ See appended electronic signature page }

Michele Fedowitz, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division /Division Director/ Harpreet Singh, M.D.
Review Division /Project Manager/Stacie Woods, RPM.
Review Division/Cross Discipline Team Lead/ Erin Larkins, M.D.
Review Division/Clinical Reviewer/ Luckson, Mathieu M.D.
OSI/Office Director/Dave Burrow
OSI/DCCE/ Division Director/Ni Aye Khin, M.D.
OSI/DCCE/Branch Chief/Kassa Ayalew, M.D.
OSI/DCCE/Acting Team Leader/Karen Bleich, M.D.
OSI/DCCE/GCP Reviewer/Michele Fedowitz, M.D.
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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KASSA AYALEW
11/12/2020 12:21:20 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: October 15, 2020
Requesting Office or Division: Division of Oncology 2 (DO2)
Application Type and Number: NDA 214096
Product Name and Strength: Tepmetko (tepotinib) Tablets, 225 mg
Applicant/Sponsor Name: EMD Serono Research and Development Institute Inc
OSE RCM #: 2020-1104-1
DMEPA Safety Evaluator: Janine Stewart, PharmD
DMEPA Team Leader: Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 7, 2020 for Tepmetko. Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Tepmetko (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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^a Stewart J. Label and Labeling Review for Tepmetko (NDA 214096). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 29. RCM No.: 2020-1104.

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JANINE A STEWART
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10/15/2020 11:28:33 AM

Interdisciplinary Review Team for Cardiac Safety Studies
QT Study Review

Submission	NDA 214096
Submission Number	006
Submission Date	6/29/2020
Date Consult Received	7/7/2020
Drug Name	Tepotinib
Indication	Advanced NSCLC with METex14 skipping alterations
Therapeutic dose	450 mg orally once daily with food
Clinical Division	DO2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 7/7/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 128073 dated 01/21/2020 in DARRTS;
- Proposed [label](#) (Submission 0006);
- [Integrated ECG report](#) and [addendum](#) (Submission 0006);
- Study VISION [ECG report](#) (Submission 0006);
- [Summary of clinical pharmacology](#) (Submission 0002);
- [Summary of clinical safety](#) (Submission 0002); and
- [Highlights of clinical pharmacology and cardiac safety](#) (Submission 0006).

1 SUMMARY

No large QTc prolongation effect (i.e., >20 msec) of tepotinib was observed in this QT assessment. Without a positive control, large clinical exposure margin or double-negative safety pharmacology studies conducted under best practices (see S7b Q&As), we are reluctant to conclude lack of a QTc effect.

The effect of tepotinib was evaluated in studies EMR200095-001, EMR200095-003, EMR200095-004, EMR200095-005, and MS200095-0022 (i.e. studies 001, 003, 004, 005, and 0022). The highest dose evaluated was 1400 mg QD, which covers the therapeutic exposure. The data were analyzed using concentration-response analysis as the primary analysis, which did not suggest that tepotinib is associated with large mean increases in the QTc interval (refer to section 4.5) – see Table 1 for overall results. The findings of this analysis are further supported by the by-time analysis (section 4.3).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)[#]

Study Identifier	Treatment groups*	Study Day	Tepotinib (ng/mL)	ΔQTcF (msec)	90.0% CI (msec)
200095001	<500 mg	Cycle 1 Day 14	241.8	0.8	(-0.6 to 2.2)
200095001	500 mg	Cycle 1 Day 14	1070.9	3.3	(1.2 to 5.4)

200095001	>500 mg	Cycle 1 Day 14	1301.4	4	(1.5 to 6.5)
Reported Cmax at 500 mg QD			1291.0	4	(1.5 to 6.4)

Based on linear mixed effect modeling of data from study 001 alone. Refer to section 4.5 for details about the reviewer's analysis.

* Therapeutic dose in the proposed product label (450 mg QD) is expressed as base equivalent of the recommended therapeutic dose in previous IRT review (500 mg QD for the salt form). Dose levels in this review are reported for the salt form.

In concentration-QTc analyses based on study 001 alone, studies 001, 003, and 004 combined, or study 0022 alone, positive concentration-QTc relationships were identified between Δ QTcF and tepotinib exposure. The highest exposure scenario known to date is when tepotinib is taken with a high fat meal (2-fold increase in exposure). The proposed therapeutic dosing regimen is oral administration with food. The PK and safety of tepotinib in patients with severe organ impairment have not been studied.

Although no large mean QTc increases were detected, in the VISION trial (cohorts A+C) 4 patients (2.2%) experienced a QTcF prolonged to > 500 msec and 10 patients (5.5%) had a QTcF prolonged by at least 60 msec from baseline.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0006. Our changes are highlighted (addition, ~~deletion~~) for suggestions only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At the recommended dosing regimen, no large mean increases in QTc (i.e. > 20 ms) were detected in patients with various solid tumors. A concentration-dependent increase in QTc interval was observed. The QTc effect of tepotinib at high clinical exposures has not been evaluated.

(b) (4)

(b) (4)

Reviewer's comment:

- While the pooled analysis included a wide dose range, the number of subjects was limited and drug exposure does not appear to increase dose proportionally at high dose levels (>500 mg). Therefore (b) (4) we recommend commenting on drug effect at the recommended dose level.
- As the included studies did not include appropriate placebo control and lacks adequate exposure margin, (b) (4) we recommend reporting a lack of large mean increases (i.e. 20 msec) on the QTc interval.
- Although a lack of large mean increase was concluded at the proposed therapeutic dose level, the sponsor considers QT prolongation to be an important potential risk for tepotinib and included categorical outliers in section 12.2.

3 SPONSOR'S SUBMISSION**3.1 OVERVIEW****3.1.1 Clinical**

Previously the sponsor proposed to conduct an integrated ECG evaluation of tepotinib and its metabolite, MSC2571109A, based on studies EMR200095-001, EMR200095-003, EMR200095-004, and EMR200095-005 (i.e. studies 001, 003, 004, and 005). The IRT raised concerns regarding ECG quality and provided recommendations regarding by-timepoint analysis and categorical analysis. It was concluded that the adequacy of the QT assessment plan would be a review issue (Previous IRT review under IND 128073 dated 01/21/2020 in DARRTS).

In the current submission, the sponsor provided an integrated ECG evaluation report based on the 4 studies and an ECG report for study VISION.

- The primary analysis (concentration-QTc analysis of QTcF) remained the same for the integrated ECG evaluation based on 4 clinical trials. The sponsor provided an addendum in response to IRT's comments on by-timepoint and categorical analyses.
- Study VISION (MS200095-0022) is a Phase 2, single arm study in patients with advanced NSCLC with METex14 skipping alterations. A central ECG laboratory conducted concentration-QTc analysis on data in Cohort A. In this study, triplicate ECGs were recorded at predose (within 30 minutes prior to dose) and at 4 hours ± 12 minutes postdose on Cycle 1 Day 1 and Cycle 2 Day 1. Single ECGs were collected at screening and on Cycle 3 Days (predose) and in every third cycle through Cycle 15. 107 patients on 500 mg QD doses were included in the PK-ECG analysis set.

The proposed therapeutic dose is expressed as 500 mg QD (salt form) at the time of previous IRT review and 450 mg QD (base equivalent) in the NDA submission. Dose levels in this review are expressed in the salt form. A summary of clinical pharmacology properties is provided below:

- Steady state exposure (geometric mean and geometric CV%) is reported to be 1291 ng/mL (48.1%) (C_{max}) or 27.4 ug*h/mL (51.7%) (AUC_{tau}) at the 500 mg QD dose level. The sponsor reported dose-proportional PK up to 500 mg QD.
- Median effective half-life is above 30 hours for tepotinib and its major metabolites. Low PK fluctuation is expected at steady state.
- Tepotinib is metabolized in humans with metabolites accounting for 48% of recovered drug-related radioactivity. Tepotinib is mainly excreted via feces (~85%).
- The sponsor claims a lack of clinically meaningful effect of age, body weight, sex, Japanese ethnicity, mild or moderate hepatic impairment (Child-Pugh Class A and B), mild or moderate renal impairment, P-gp inhibitor, proton pump inhibitor (omeprazole), or opioid analgesics, on tepotinib exposure. The PK and safety of tepotinib in patients with severe organ impairment has not been studied. The DDI potential as a victim due to co-administration of drug metabolizing enzymes is low. Food increases tepotinib exposure by approximately 2-fold.

3.1.2 Nonclinical Safety Pharmacology Assessments

Tepotinib inhibited Kv11.1 (hERG) with an IC₅₀ of 1.2 μM, i.e. 10-fold and 24-fold higher than the highest individual and the mean unbound concentrations after administration of the clinical dose of 500 mg, respectively. Other key cardiac ion channels were not inhibited or only slightly inhibited up to the highest tested concentration of 10 μM. No relevant inhibition of key cardiac ion channels were found for MSC2571109A.

No relevant effects were seen in dedicated cardiovascular safety pharmacology studies in rats and dogs. In addition, arterial blood pressure and ECG parameters were measured in the repeat-dose toxicity studies in dogs (up to 39 weeks). No treatment-related changes were found up to the highest dose of 30 mg/kg where mean free C_{max} of 15.2 ng/mL (males) and 33.2 ng/mL (females) were achieved. These exposures are in a similar range to the calculated mean free steady-state C_{max} in patients of 25.8 ng/mL at the clinical dose of 500 mg.

Reviewer's comment: Safety pharmacology studies were not conducted according to best practices and do not support an integrated risk assessment per ICH S7B Q&A 1.1-1.2.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for tepotinib was based on exposure-response analysis. Please see section 3.2.3 for additional details.

The sponsor provided descriptive statistics for each dose level for each study.

Reviewer's comment: FDA reviewer performed parametric descriptive statistics (mean, CI) for by-time analysis for 500 mg dose group (therapeutic dose) and presented together for different formulation which shows that all upper bounds are less than 20 msec. Please see section 4.3 for details.

3.2.1.1 Assay Sensitivity

Not Applicable

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

Per the sponsor's analysis, there were 7 subjects who experienced QTcF > 500 msec and 3 subjects who experienced Δ QTcF > 60 msec.

Reviewer's comment: FDA reviewer's analysis results are not directly comparable to the sponsor's analysis results. The categorical analysis was conducted using the safety population and included all postdose data both scheduled and unscheduled ECGs. The sponsor used a subset of the data for their categorical analysis. Categorical analysis of pooled dose across studies showed that there were 8 subjects with QTcF > 500 msec in 500 mg dose group and 12 subjects with Δ QTcF > 60 msec. FDA reviewer could not locate the categorical analysis of other intervals. FDA reviewer performed categorical analysis for HR, PR and QRS too. Please see section 4.4 for additional details.

3.2.3 Exposure-Response Analysis

In the integrated analysis of 4 studies, the sponsor assessed homogeneity and noted the difference in the estimated slope between study 005 and three other trials. The sponsor considered 2 subjects in study 005 and 1 subject in study 004 as outliers because these subjects showed high QTcF shortening (>3x SD or -75 msec). After excluding these 3 subjects, a linear mixed effect model with baseline and tepotinib concentration as fixed effects was used for evaluating the effect of tepotinib on QTcF; a multivariate linear mixed effect model with baseline, tepotinib concentration, MSC2571109A concentration and the interaction term between tepotinib and MSC2571109A concentration was also evaluated. Models were compared using the AIC criterion. In the final model (tepotinib alone), the estimated population mean slope for the tepotinib concentration was 3.2 msec/(ug/mL) (p = 0.01). The upper bound of 90% CI at an estimated steady state Cmax (1818.5 ng/mL) was 7.54 msec. In the model with tepotinib and metabolite concentration, the estimated slopes were not statistically significant at p=0.05.

For study 0022, a prespecified linear mixed effects model (Δ QTcF ~ 1 + centered baseline + tepotinib concentration, random effects on intercept and slope) was applied. The slope for plasma concentration of tepotinib versus Δ QTcF was 7.132 msec/ug/mL (p = 0.0051). The estimated intercept was -4.4 msec (90% CI: -7.3 to -1.5 msec). At the popPK model-derived mean steady-state Cmax (1236 ng/mL, 500 mg QD), the predicted mean Δ QTcF was 4.4 msec and the upper bound of its 90% confidence interval was 7.9 msec. When considering concentration of parent drug, metabolite and interaction effect, the estimated intercept and slopes were not statistically significant at p=0.05.

Reviewer's comment: The reviewer used tepotinib concentration as the only exposure covariate because the time course of metabolite and parent drug exposure are similar in this study (data not shown) and there was no prior knowledge to suggest an effect by the major metabolite. The reviewer applied the pre-specified linear model on data from

studies 001, 003, 004, and 005. The reviewer's estimates of concentration-QTc slopes from the pooled dataset and study 0022 are similar to the sponsor's. Refer to section 4.5 for details about the reviewer's analysis.

3.2.4 Cardiac Safety Analysis

Sponsor's Tables 44 and 45 in module 2.7.4 Summary of Safety show the numbers of patients experiencing QTc prolongation and AEs related to QTc prolongation.

Table 44 Summary of On-treatment QT Prolongation Findings

QT Prolongation Findings	Tepotinib 500 mg qd -- SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
Any on-treatment QTcF > 500 ms	4 (2.2)	9 (2.4)
On-treatment QTcF > 500 ms (baseline ≤ 450 ms)	2 (1.1)	2 (0.5)
On-treatment QTcF > 500 ms (baseline > 450 ms - ≤ 480 ms)	0	1 (0.3) a
On-treatment QTcF > 500 ms (baseline > 480 ms - ≤ 500 ms)	0	1 (0.3) a
On-treatment QTcF > 500 ms (baseline > 500 ms)	1 (0.6) b	4 (1.1) b
On-treatment QTcF > 500 ms (baseline unknown)	1 (1.1)	1 (0.3)
On-treatment QTcF prolonged by > 60 ms	10 (5.5)	14 (3.8)

Source: ISS Tables 12.8.2.1.2.1. and 12.8.2.1.1.1.

SAF = Safety Analysis Set. Footnotes are derived from a review of the patient level data.

a 1 had baseline QTcF of > 480 ms and a single on-treatment reading that was > 500 ms; the other had relevant concurrent events and concomitant medication that provided a clear alternative cause.

b No on-treatment worsening

Table 45 Treatment Emergent Adverse Events Related to QTc Prolongation

Primary System Organ Class Preferred Term	Tepotinib 500 mg qd -- SAF	
	VISION Cohorts A + C (N=181) n (%)	POOL (N=373) n (%)
Patients with at least one event	9 (5.0)	16 (4.3)
Investigations	6 (3.3)	10 (2.7)
Electrocardiogram QT Prolonged	6 (3.3)	10 (2.7)
Nervous system disorders	2 (1.1)	5 (1.3)
Syncope	1 (0.6)	3 (0.8)
Generalised tonic-clonic seizure	0	1 (0.3)
Loss of consciousness	1 (0.6)	1 (0.3)
Cardiac disorders	1 (0.6)	1 (0.3)
Long QT syndrome	1 (0.6)	1 (0.3)

Source: ISS Table 12.8.2.3.1.

Reviewer's comment: Although concentration-QTc analysis did not suggest risk for QTc prolongation, there were 3 reported AEs from VISION cohorts A + C (b) (6) (b) (5) which describe multiple episodes of QTc prolongation occurring on-treatment and without conclusive alternative explanations for these QTc effects. In addition, 3 patients (b) (6) who experienced single episodes of QTcF from baseline of > 60 ms, did not involve notable alternative explanations for QT prolongation other than mild electrolyte abnormalities.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable as no large increases or decreases in heart rate (i.e. $|\text{mean}| < 10$ beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Paper ECGs for Study 001 were submitted, but ECGs for Study 003, 004, and 005 were not due to the COVID-19 outbreak. Waveforms for Study 0022 from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study (0022) appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

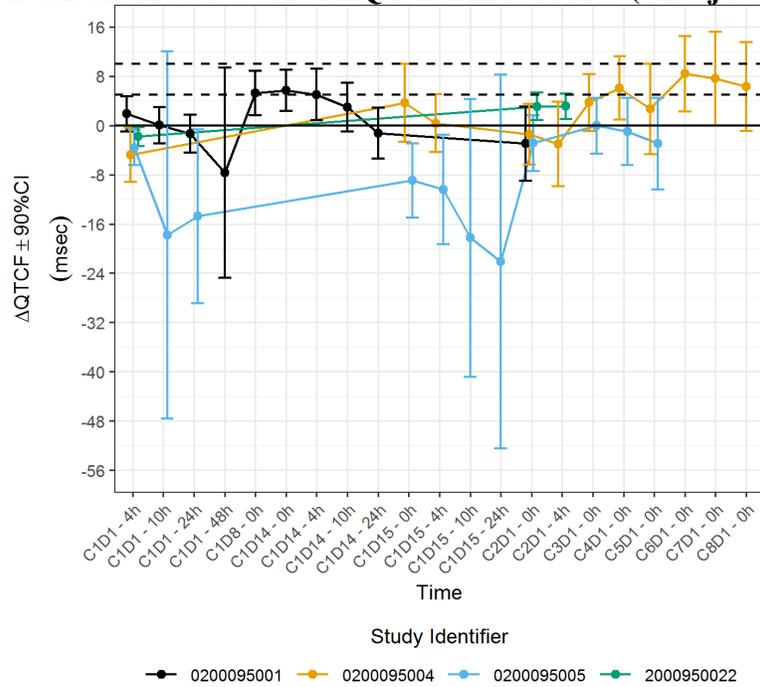
Among five studies (Study IDs: 0200095001, 0200095003, 0200095004, 0200095005 and 2000950022), four studies were included in by-time analysis. Study 0200095003 was excluded due to small sample size ($n=6$). The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer evaluated the ΔQTcF effect using parametric descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for 500 mg dose group (therapeutic dose) by different studies.

Figure 1: Mean and 90% CI of Δ QTcF Time Course (unadjusted CIs).



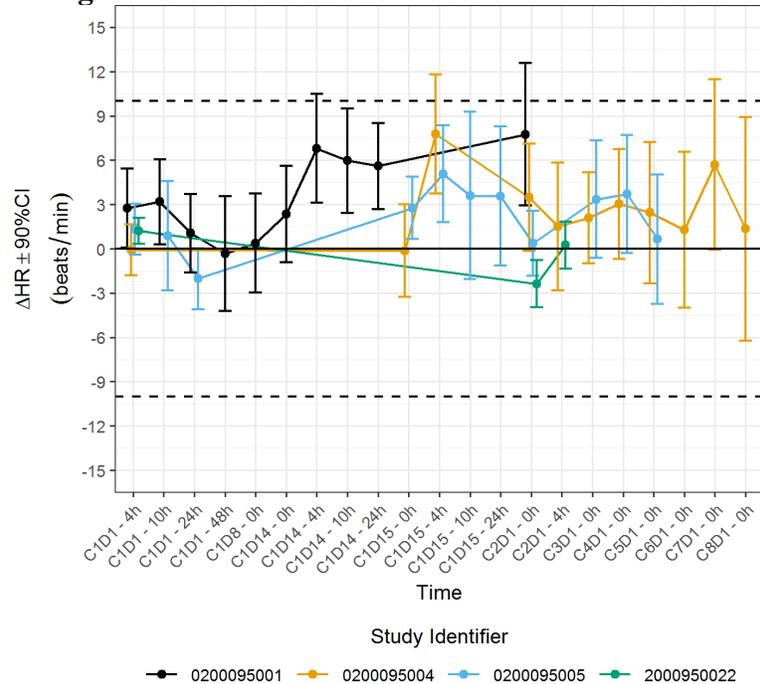
4.3.1.1 Assay sensitivity

Not Applicable.

4.3.2 HR

Figure 2 displays the time profile of Δ HR for 500 mg dose group (therapeutic dose) by different studies.

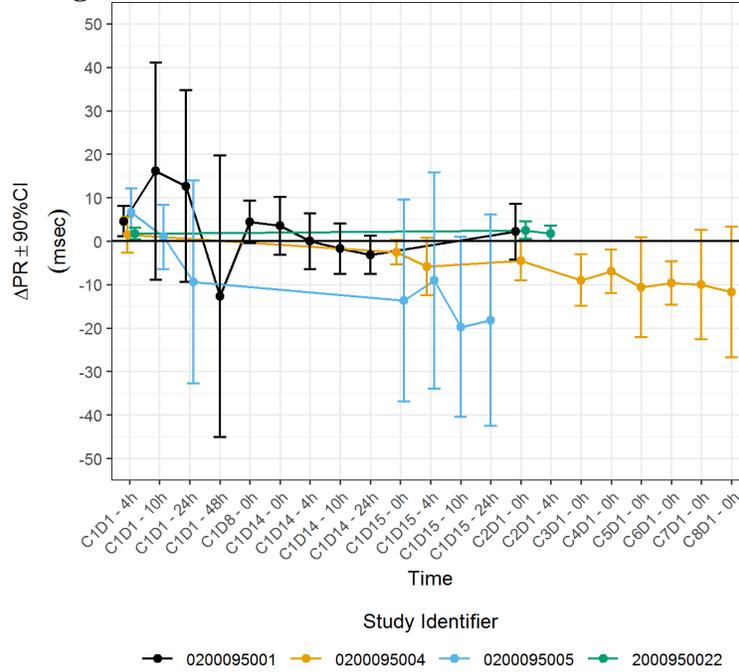
Figure 2: Mean and 90% CI of Δ HR Time Course



4.3.3 PR

Figure 3 displays the time profile of Δ PR for 500 mg dose group (therapeutic dose) by different studies

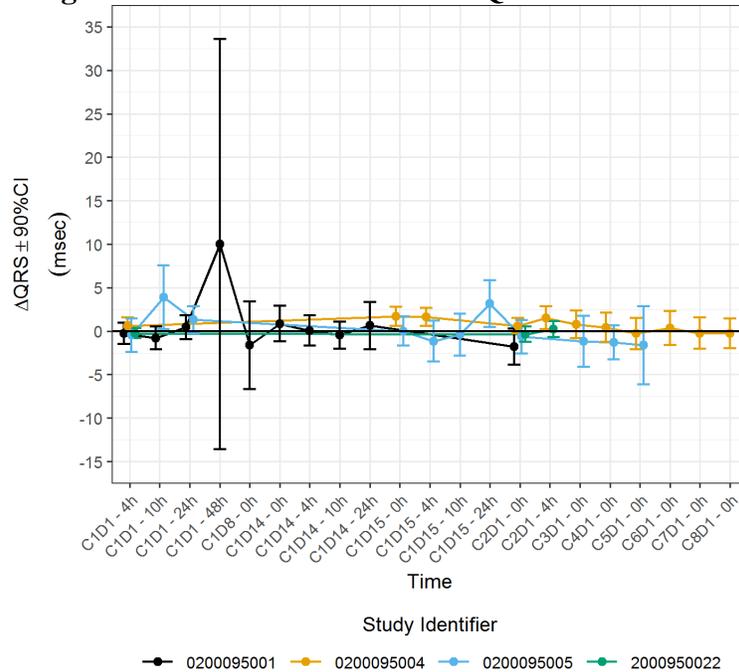
Figure 3: Mean and 90% CI of Δ PR Time Course



4.3.4 QRS

Figure 4 displays the time profile of Δ QRS for 500 mg dose group (therapeutic dose) by different studies.

Figure 4: Mean and 90% CI of Δ QRS Time Course



4.4 CATEGORICAL ANALYSIS

All five studies (studies 001, 003, 004, 005 and 0022) were included in the categorical analysis. Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs. To minimize dose groups, <500 mg, 500 mg and >500 mg dose levels were pooled together across studies. If a category is omitted from the categorical analysis table, that means that no subjects had values in that category.

4.4.1 QTc

Table 2 lists the number of subjects as well as the number of observations whose QTc values were ≤ 450 msec, between 450 and 480 msec, between 480 and 500 msec and greater than 500 msec with or without a change from baseline greater than 60 msec. There were eight subjects who experienced QTcF greater than 500 msec and among them two subjects had the changes from baselines greater than 60 msec in 500 mg dose group.

Table 2: Categorical Analysis for QTcF (maximum)

TRTAGR1	Total (N)		Value ≤ 450 msec		450 msec < Value ≤ 480 msec		480 msec < Value ≤ 500 msec		Value > 500 msec & < 60 msec		Value > 500 msec & ≥ 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
<500 mg	106	989	85 (80.2%)	894 (90.4%)	18 (17.0%)	64 (6.5%)	3 (2.8%)	31 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
500 mg	342	2567	267 (78.1%)	2304 (89.8%)	58 (17.0%)	231 (9.0%)	9 (2.6%)	19 (0.7%)	6 (1.8%)	11 (0.4%)	2 (0.6%)	2 (0.1%)
>500 mg	23	258	23 (100.0%)	258 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 3 lists the categorical analysis results for ΔQTcF (less than 30 msec, between 30 and 60 and greater than 60 msec). There was one subject in <500 mg dose group and eleven subjects in 500 mg dose group who experienced ΔQTcF greater than 60 msec.

Table 3: Categorical Analysis for ΔQTcF (maximum)

TRTAGR1	Total (N)		Value ≤ 30 msec		30 msec < Value ≤ 60 msec		Value > 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
<500 mg	106	989	90 (84.9%)	962 (97.3%)	15 (14.2%)	26 (2.6%)	1 (0.9%)	1 (0.1%)
500 mg	342	2567	273 (79.8%)	2405 (93.7%)	58 (17.0%)	149 (5.8%)	11 (3.2%)	13 (0.5%)
>500 mg	23	258	22 (95.7%)	255 (98.8%)	1 (4.3%)	3 (1.2%)	0 (0%)	0 (0%)

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were thirty two subjects in <500 mg dose group, fifty seven subjects in 500 mg dose group, and seven subjects in >500 mg dose group who experienced HR greater than 100 beats/min.

Table 4: Categorical Analysis for HR (maximum)

TRTAGR1	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
<500 mg	106	991	74 (69.8%)	915 (92.3%)	32 (30.2%)	76 (7.7%)
500 mg	344	2017	287 (83.4%)	1890 (93.7%)	57 (16.6%)	127 (6.3%)
>500 mg	23	258	16 (69.6%)	244 (94.6%)	7 (30.4%)	14 (5.4%)

4.4.3 PR

Table 5 lists the categorical analysis results for PR (less than 200 msec; between 200 and 220 msec, and above 220 msec with and without 25% increase over baseline). There was one subject in <500 mg dose group and six subjects in 500 mg dose group who experienced PR greater than 220 msec and the changes from baselines were greater than 25% msec.

Table 5: Categorical Analysis for PR

TRTAGR1	Total (N)		Value <= 220 msec		Value > 220 msec & < 25%		Value > 220 msec & >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
<500 mg	103	942	101 (98.1%)	935 (99.3%)	1 (1.0%)	6 (0.6%)	1 (1.0%)	1 (0.1%)
500 mg	247	1822	231 (93.5%)	1771 (97.2%)	10 (4.0%)	42 (2.3%)	6 (2.4%)	9 (0.5%)
>500 mg	23	256	23 (100.0%)	256 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

4.4.4 QRS

Table 6 lists the categorical analysis results for QRS (less than 120 msec and above 120 msec with and without 25% increase over baseline). There were two subjects who experienced QRS greater than 120 msec and the changes from baselines were greater than 25% msec in 500 mg dose level.

Table 6: Categorical Analysis for QRS

TRTAGR1	Total (N)		Value <= 120 msec		Value > 120 msec & < 25%		Value > 120 msec & >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
<500 mg	106	990	102 (96.2%)	933 (94.2%)	4 (3.8%)	57 (5.8%)	0 (0%)	0 (0%)
500 mg	346	2681	306 (88.4%)	2465 (91.9%)	38 (11.0%)	203 (7.6%)	2 (0.6%)	13 (0.5%)
>500 mg	23	258	22 (95.7%)	254 (98.4%)	1 (4.3%)	4 (1.6%)	0 (0%)	0 (0%)

4.5 EXPOSURE-RESPONSE (E-R) ANALYSIS

The primary analysis was conducted using data from studies 001, 003, 004, and 005. Sensitivity analysis were conducted using data from 001 alone, studies 001, 003, and 004 combined (excluding one subject who had $\Delta\text{QTcF} < -75$ msec), or study 0022 alone. E-R analyses were conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK (i.e. within 60 min of ECG recording). Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key

assumptions of the model needs to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) delay between plasma concentration and Δ QTc and 3) presence of non-linear relationship. A pre-specified linear mixed effect model, Δ QTcF \sim 1 + centered baseline + tepotinib with random effect on the intercept and slope, was applied.

4.5.1 QTc

A total of 286 subjects from studies 001, 003, 004, and 005 were included in the primary E-R analysis. Study dose ranged from 60-1400 mg QD. 104, 159, and 23 subjects received <500 mg, 500 mg, or <500 mg QD doses.

Figure 2 shows the time-course of $\Delta\Delta$ HR, which shows an absence of significant $\Delta\Delta$ HR changes. Figure 5 shows the time-course of drug-concentration and Δ QTc at 500 mg QD dose in the first 2 cycles, suggesting moderate accumulation, low fluctuation in tepotinib exposure at steady state, and a lack of signs for significant hysteresis. The time-course of Δ QTc in study 005 separates from the other 3 studies. Figure 6 shows the relationship between drug exposure and Δ QTc and generally supports the use of a linear model. There were outlier observations with significant QTc decrease in studies 005 and 004 (Δ QTcF < -100 msec). The linear regression lines in studies 001, 003 and 004 largely overlays with each other while that in study 005 appears separated. The linear mixed effect model does not suggest a statistically significant slope. The goodness-of-fit plot is shown in Figure 7.

Figure 5: Time course of drug concentrations and QTc.

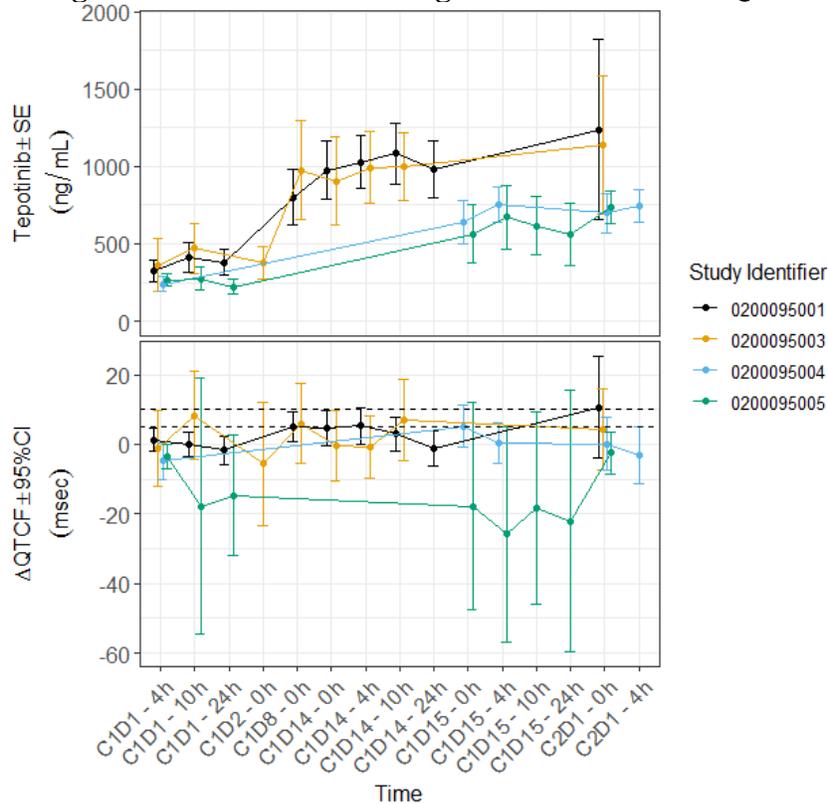


Figure 6: Assessment of linearity of concentration-QTc relationship

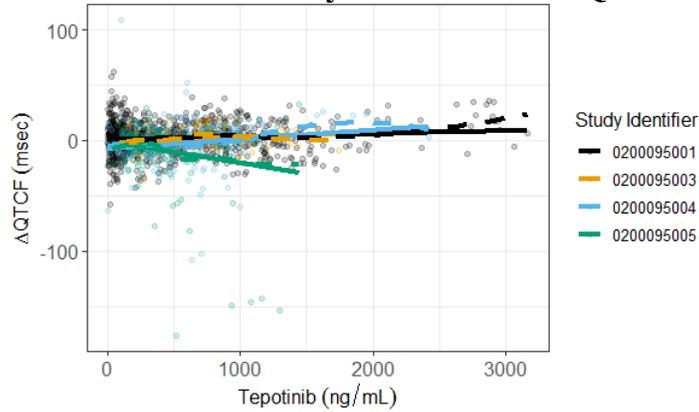
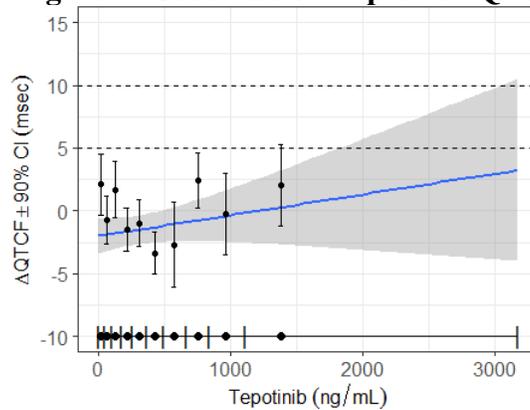
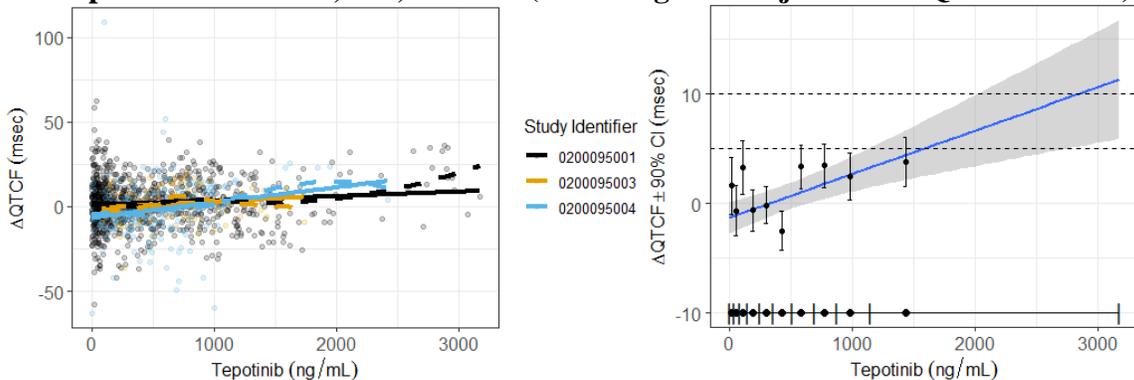


Figure 7: Goodness-of-fit plot for QTc



In sensitivity analyses, after excluding study 005 and subject (b) (6) in study 004, the linearity plot and goodness-of-fit plot are shown in Figure 8. The linear mixed effect model suggests a statistically significant concentration-QTc slope (3.97 msec per ug/mL; p-value < 0.001), however, the upper bound of 90% confidence interval of predicted QTc increase is less than 10 msec at the steady state C_{max} for the proposed therapeutic dose (upper bound CI: 5.9 msec at 1291 ng/mL).

Figure 8: Assessment of linearity of concentration-QTc relationship and goodness-of-fit plot in studies 001, 003, and 004 (excluding one subject with ΔQTc < -75 msec).



Similar results were obtained when the analysis was conducted using data from study 001 or study 0022 alone (Figure 9 and Figure 10). The estimated concentration-QTc slope was

3.03 or 7.30 msec per ug/mL in study 001 or study 0022, respectively, however, the predicted Δ QTc values were less than 10 msec at the therapeutic dose. The estimated intercept was negative in the model developed with study 0022 alone.

Figure 9: Assessment of linearity of concentration-QTc relationship and goodness-of-fit plot for QTc in study 001.

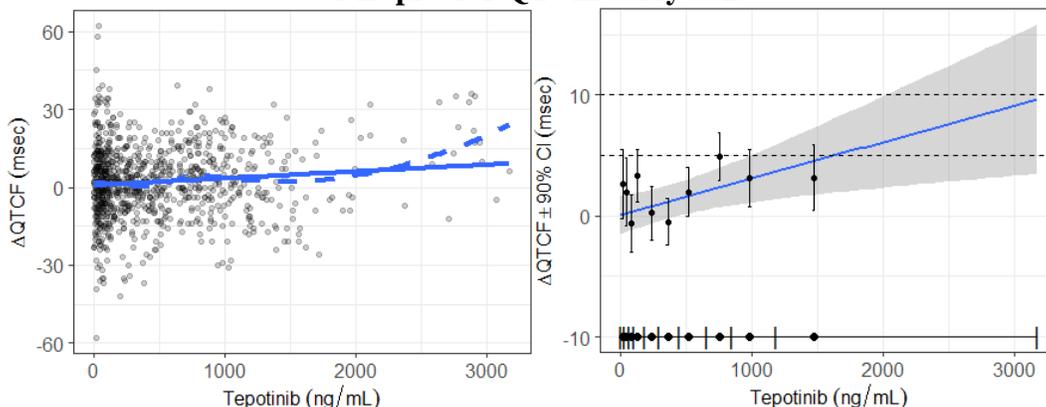
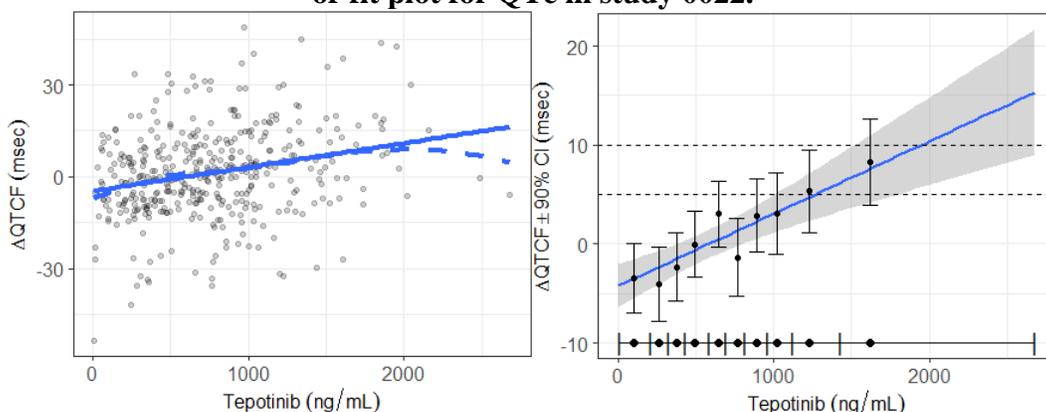


Figure 10: Assessment of linearity of concentration-QTc relationship and goodness-of-fit plot for QTc in study 0022.



Overall, the primary E-R analysis and sensitivity analyses suggest that tepotinib treatment does not cause large mean increases at the proposed therapeutic dose ($C_{\max,ss}$: 1291 ng/mL). While the primary analysis does not suggest a positive E-R relationship between Δ QTcF and tepotinib concentration, the observation could have been affected by the presence of potential outliers in studies 004 and 005 and variations across studies. On the other hand, of the 148 subjects receiving 30-1400 mg doses in study 001, 59 subjects received doses at or above 500 mg QD. Study 001 alone has adequate sample size and exposure to support a QT assessment to exclude large mean effects at the 500 mg QD dose. The estimated positive E-R relationship is plausible as suggested by a low safety margin from nonclinical studies, and the final model shows reasonable parameter estimate and goodness-of-fit. Therefore, we propose to report the QTc effect as predicted by the concentration-QTc analysis based on study 001 alone (Table 1).

4.5.1.1 Assay sensitivity

Not applicable.

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.

/s/

NAN ZHENG
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FERDOUSE BEGUM
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DALONG HUANG
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MICHAEL Y LI
10/06/2020 11:24:05 AM

LARS JOHANNESSEN
10/06/2020 02:07:19 PM

CHRISTINE E GARNETT
10/06/2020 02:51:25 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 29, 2020
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214096
Product Name, Dosage Form, and Strength:	Tepmetko (tepotinib) Tablets, 225 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	EMD Serono Research and Development Institute Inc
FDA Received Date:	June 29, 2020
OSE RCM #:	2020-1104
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the review process for this NDA, this review evaluates the proposed Tepmetko prescribing information (PI), Patient Information, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, Patient Information, container label, and carton labeling for Tepmetko (tepotinib) to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the container label and carton labeling that can be modified to improve the clarity of the information presented.

4 CONCLUSION & RECOMMENDATIONS

The proposed Tepmetko PI and Patient Information are acceptable from a medication error perspective. The proposed container label and carton labeling can be improved to clearly present important product information, reduce redundancy, and to promote the safe and effective use of the proposed product. We provide recommendations for EMD Serono Research and Development Institute Inc in Section 4.1 below.

4.1 RECOMMENDATIONS FOR EMD SERONO RESEARCH AND DEVELOPMENT INSTITUTE INC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Container Labels

1. To minimize confusion and reduce the risk for deteriorated drug medication errors, revise the blister label to include lot number and the expiration date information.
 - a. See recommendation A.1
2. To reduce redundancy and allow space to enlarge important product information for improved prominence and readability:
 - a. Remove (b) (4)
 - b. Increase the font size of the proprietary name, established name with dosage form, and the strength statements.

C. Carton Labeling

1. The proposed carton labeling utilizes a different color scheme to differentiate between the 2 packaging configurations (i.e., 30 and 60 tablet count) of products of the same 225 mg strength. The use of different color schemes to denote different packaging configurations within the product line of a single strength product is uncustomary and suggests a difference in strength which may lead to confusion. The "30 tablets" and "60 tablets" net quantity statements serve to differentiate the packaging configurations within the product line. Revise the container labels to use a single color scheme for both packaging configurations.
2. The net quantity statement and the surrounding graphic in the lower left corner of the PDP compete for prominence with the proprietary name, established name and the strength statement. Increase the prominence of the proprietary name, established name and the strength statement taking into account all

pertinent factors; including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

- a. Ensure the established name is at least half the size of the proprietary name to be in accordance with 21 CFR 201.10(g)(2).
3. Remove (b) (4)
Revise the remainder of the description to read "Each carton contains 3 child-resistant blister cards of 10 tablets each" to appear adjacent to the existing quantity statement that appears in the lower left corner of the PDP.
 - a. Revise the 60 tablet configuration accordingly.
 4. To reduce clutter on the PDP and ensure consistency with the Prescribing Information (PI), revise and relocate the (b) (4) statement to read "Recommended Dosage: See prescribing information." and to appear on the back panel.
 5. Remove (b) (4) information that appears on the back panel. That information is not required to appear on the carton labeling.
 6. To simplify and improve the readability, revise the storage information to read "Storage: 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP-NF Controlled Room Temperature]. Store in original package".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tepmetko received on June 29, 2020 from EMD Serono Research and Development Institute Inc.

Table 2. Relevant Product Information for Tepmetko	
Initial Approval Date	N/A
Active Ingredient	tepotinib
Indication	For the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) [REDACTED] (b) (4) [REDACTED]
Route of Administration	Oral
Dosage Form	Tablets
Strength	225 mg
Dose and Frequency	450 mg orally once daily with food; may reduce dose to 225 mg orally once daily for adverse reactions
How Supplied	Box of 30 tablets: 3 blister cards each containing 10 tablets Box of 60 tablets: 6 blister cards each containing 10 tablets
Storage	Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP-NF Controlled Room Temperature]. Store in original package.
Container Closure	The primary packaging is a transparent blister consisting of a form foil and a lidding foil with child-resistant feature. The secondary packaging is composed of printed cartons.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Tepmetko labels and labeling submitted by EMD Serono Research and Development Institute Inc.

- Unit-Dose Blister labels received on June 29, 2020
- Unit-Dose Carton Labeling received on June 29, 2020
- Prescribing Information (Image not shown) received on June 29, 2020, available from <\\CDSESUB1\evsprod\nda214096\0006\m1\us\114-labeling\114a-draft-label\prescribing-information-word.docx>

G.2 Label and Labeling Images

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JANINE A STEWART
09/29/2020 09:42:39 AM

ASHLEIGH V LOWERY
09/29/2020 10:07:14 AM