CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214096Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

NDA 214096

Review # 01

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: (b) (4) months for the drug substance packaged in the proposed commercial package when stored at (b) (4) temperature

FDA Assessment: Retest date of (b) (4) months may be granted when stored at the proposed storage conditions.

Drug Product Expiration Dating Period: 30 months for the drug product packaged in the proposed commercial package when stored at room temperature

FDA Assessment: An expiration dating period of 30 months may be granted when stored at the proposed storage conditions.

[Applicant will complete this section.]

Drug Name/Dosage Form	Tepotinib film-coated tablets
Strength	225 mg tepotinib (250 mg tepotinib hydrochloride hydrate)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	Non-small cell lung cancer
Applicant	EMD Serono Research and Development Institute
US agent, if applicable	Not applicable

[FDA will complete these sections.]

Submit Date(s)	June 29, 2020
Received Date(s)	June 29, 2020
PDUFA Goal Date	February 28, 2021

FDA assessment is indicated in blue colored fonts

Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	October 30, 2020
Established Name	Tepotinib
(Proposed) Trade Name	TEPMETKO
Pharmacologic Class	kinase inhibitor
Recommendation on Regulatory Action	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	*06/29/2020*	*CMC*
Quality Information	*07/02/2020*	*OPMA*
Quality Amendment	*07/30/2020*	*DP*
Quality Amendment	*08/05/2020*	*DP*
Quality Amendment	*08/20/2020*	*OPMA*
Quality Amendment	*09/15/2020*	*OPMA*
Labeling	*09/18/2020*	*DP*
Quality Amendment	*10/06/2020*	*OPMA*
Labeling	*10/07/2020*	*DP*
Labeling	*10/19/2020*	*DP*
Quality Amendment	*10/23/2020*	*OPMA*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Kabir Shahjahan	Ali H. Al Hakim
Drug Product	Olen Stephens	Anamitro Banerjee
Process and Facility	Zhijin Chen	Bogdan Kurtyka
Biopharmaceutics	Mei Ou	Banu Zolnik
Regulatory Business Process Manager	Kristine Leahy	N/A
Application Technical Lead	Xing Wang	N/A
ORA Lead	N/A	
Environmental	James Laurenson	N/A

ORBIS Partner Agency Quality Review Team ***(To be redacted for FOIA)***

Agency	PRIMARY REVIEWER	SECONDARY REVIEWER
HC Canada		
HSA Singapore		
TGA Australia		
Swissmedic Switzerland		

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	Type III		(b) (4)	**Adequate**	Active; supports several approved A/NDA's
	Type III			**Adequate**	Active; supports several approved A/NDA's

Other Documents: *IND, RLD, or sister applications*

[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A	IND 106,103	Original IND submitted on September 1, 2009; the IND May Proceed letter was received on October 2, 2009.
N/A	IND 128,073	IND 128,073 was submitted on February 11, 2016; the IND May Proceed letter was received on March 11, 2016.

CONSULTS

None

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Evaluation of the Quality Information

1. EXECUTIVE SUMMARY

[FDA will complete this section.]
Tepotinib is a reversible, Type I, adenosine triphosphate (ATP)-competitive inhibitor of the receptor tyrosine kinase mesenchymal-epithelial transition factor (MET).

Tepotinib drug substance is manufactured [redacted (b) (4)] The proposed DS specifications are acceptable. The proposed impurity levels for three specified related impurities are qualified. Analytical methods are adequately validated. All methods except for the HPLC and Headspace-GC methods are compendial. Retest date of [redacted (b) (4)] months may be granted when stored at the proposed storage conditions.

The drug product is an immediate-release film-coated tablet for oral administration, containing 250 mg tepotinib hydrochloride hydrate (equivalent to 225 mg tepotinib). The formulation uses all compendial excipients or excipients composed of compendial components. Drug product specifications are acceptable. [redacted (b) (4)] content, elemental impurities and polymorph are not tested but adequately justified. The combination of methods and accompanying validation data is sufficient to assure the drug product meet the requirements for identity, strength, quality, purity, potency, and bioavailability as prescribed in 21 CFR 314.50(d)(1)(ii)(a). The finished product is packaged in a transparent blister [redacted (b) (4)] The blister has an aluminum lidding foil with child-resistant [redacted (b) (4)] feature. These blisters are packed into carton boxes. An expiration dating period of 30 months may be granted when stored at the proposed storage conditions. Note that the bulk tablets have been granted an [redacted (b) (4)] month hold time. The shelf life is determined [redacted (b) (4)]

The drug product manufacturing process consists of the following manufacturing steps: [redacted (b) (4)]
Proposed CPPs and IPCs are acceptable. The 704(a)4 document review mitigates the need of PAI at the drug product manufacturing facility. Based on the joint assessment of OPMA and ORA for the 704(a)4 documents (CMS WA 349034), drug product manufacturing facility is recommended as approval with post-approval inspection to cover the data integrity on field and major equipment calibration records. Drug substance manufacturing facility is recommended as approval per compliance history.

The proposed dissolution method (USP Apparatus II Paddle, 50 rpm, 900 mL of acetate buffer pH 4.5 with 1 mM NaCl and 0.1% polysorbate 80) has acceptable discriminating

ability with regards to critical formulation variables (CFVs, i.e., (b) (4)) and TF1 and TF3 formulations/tablets produced from different manufacturing process and excipients. The proposed dissolution method is acceptable as a quality control (QC) test for the proposed Tepotinib Tablets, 225 mg, for batch release and stability testing. The proposed acceptance criterion of "Q= (b) (4) % in 15 minutes" is also acceptable.

In Vitro Formulation Bridging: i) the in vivo PK information of all formulations have been studied; ii) TF2 and TF3 formulations showed similarity in the in vitro dissolution; iii) there is no change in manufacturing process and manufacturing site for the commercial TF3 formulation; and iv) the in vivo bridging between TF2 and TF3 formulation appears to be established, therefore, no need to request additional in vivo or in vitro bridging studies among all formulations.

In conclusion, OPQ recommends APPROVAL to NDA 214096.

Life Cycle Considerations:
None

2. APPLICATION BACKGROUND

Original IND 106103 was submitted to FDA on September 1, 2009 (solid tumors). The IND May Proceed letter was received on October 2, 2009. IND 128073 (NSCLC) was submitted to FDA on February 11, 2016. The IND May Proceed letter was received on March 11, 2016.

On September 10, 2019, breakthrough therapy designation was granted for tepotinib for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors harbor MET exon 14 skipping alterations (METex14) and who progressed following platinum-based cancer therapy.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION/SUBMISSION REGULATORY ACTIVITY

The Applicant's Position:

A list of regulatory CMC interactions with FDA that are relevant for NDA 214096 is provided in Table 1.

Table 1 CMC Interactions with FDA and Pre-NDA Agreements

Interaction	Description	Pre-NDA Agreements
Type C (CMC) meeting; May 2017 (Reference ID: 4110393)	To discuss and reach agreement regarding the designation of drug substance starting materials.	• FDA agreed additional justification would not be necessary if the FDA recommendation (b) (4) is adopted. • FDA agreed the three commercially available raw materials employed (b) (4) are acceptable without further justification.
Type C, Written Feedback; September 2019 (Reference ID: 4490721)	To obtain guidance on product comparability to support introduction of a new product formulation during generation of confirmatory evidence.	• Post-meeting agreement: FDA agreed the rationale for the control of (b) (4) is reasonable. • Post-meeting agreement: FDA agreed that equivalency between DS manufactured (b) (4) (b) (4) and DS process performance qualification batches was demonstrated. • Post-meeting agreement: FDA agreed the strength representation for the manufacturing process (batch formula, composition, and assay calculations) of the DP are reasonable.
Type B, Pre-NDA (CMC) meeting; January 2020 (Reference ID: 4490721)	To discuss and reach agreement regarding the content and format of the proposed NDA as it relates to the Quality submission package, including specific agreements related to the proposed dissolution acceptance criterion of the drug product, the proposed dissolution method evaluating the drug product, the acceptability of the drug product primary registration batches for the establishment of the commercial shelf-life, the inclusion of only 250 mg TF3 dose strength as the intended commercial supply, and the overall structure of the proposed CTD Quality	• FDA accepted the DP primary registration batches which were: o packaged in an analogous blister configuration that has the same commercial aluminum lidding but does not include the child resistant feature. o manufactured (b) (4) (b) (4) • FDA agreed to the proposed overall structure of the Quality Modules and that it is acceptable to only include information for the intended commercial product in sections P.1, P.3, P.4, P.5.1-3, P.5.5-6, P.7, and P.8 of the NDA and information for previous formulations are included in other sections. • Post-meeting agreement: FDA agreed the proposed dissolution

Interaction	Description	Pre-NDA Agreements
	Modules to support an original NDA.	method is adequate for the proposed tepotinib tablets, 250 mg.

The FDA's Assessment: ***Consistent with FDA's records***

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

EMD Serono requests a categorical exclusion from the requirement to prepare an environmental assessment statement as per 21 CFR 25.31 (b) for tepotinib. As per the requirements, the Environmental Introduction Concentration (EIC) entering the aquatic environment from patient use is calculated without including consideration of metabolism or environmental depletion mechanisms that occur in the wastewater treatment process. The EIC from patient use is based on the highest annual quantity of the active moiety expected to be produced for use during the next years and the quantity used in all dosage forms and strengths.

The following calculation of the EIC for the aquatic environment assumes that all drug products produced in a year are used and enter the publicly owned treatment works (POTWs), even distribution throughout the USA per day, and no metabolism or depletion mechanisms:

EIC-aquatic (ppb) = A x B x C x D

where:

A = kg/year production (as active moiety)

B = 1 / 1.0711 x 10^{11} (1 / liters per day entering POTWs) (CWNS. 2016)

C = year / 365 days

D = 10^9 µg/kg (conversion factor)

For tepotinib, the EIC is calculated as follows:

$$EIC\ aquatic = \frac{\text{(b) (4)} \times 10^9 kg\ \mu g\ d}{1.0711 \times 10^{11} \times 365\ d\ L\ kg} = \text{(b) (4)}\ \frac{\mu g}{L}\ (ppb)$$

The EIC-aquatic from patient use of tepotinib, based on the use estimate of (b) (4) kg for the USA, is (b) (4) ppb. Because the EIC is below 1 ppb, the data are in compliance with the exclusion criteria and the tepotinib application qualifies for a categorical exclusion. To our knowledge, no extraordinary circumstances exist that require the submission of an EA.

The FDA's Assessment: ***Adequate***

The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The applicant included a use amount that was consistent with the claim and the product. The FDA EA Team reviewed the claim and determined that approval of this application would not result in significant environmental impact. The required statement of no extraordinary circumstances also was provided, in accordance with 21 CFR 25.15. Therefore, the claim for an exclusion from an EA is acceptable.

5. BIOWAIVER REQUEST/BCS DESIGNATION REQUEST

The Applicant's Position:

The NDA does not contain a biowaiver or BCS designation request.

The FDA's Assessment: ***Adequate***

Biowaiver is not needed since there is only one strength product being proposed.

6. FACILITIES

Drug substance (DS) manufacturing, packaging, and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**DUNS**	**Responsibility**	**Recommendation**
(b) (4)			

All FDA assessment is indicated in colored fonts: Executive Summary, Drug Substance, Drug Product, Environmental Assessment, labeling, Process, Facility, Biopharmaceutics, and Microbiology.

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(b) (4)

7. DRUG SUBSTANCE

a. GENERAL DESCRIPTION AND STRUCTURE

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(b) (4)

[redacted]

8. DRUG PRODUCT

a. DRUG PRODUCT DESCRIPTION AND COMPOSITION

The DP is an immediate-release film-coated tablet for oral administration, containing 250 mg tepotinib hydrochloride hydrate (equivalent to 225 mg tepotinib). The film-coated tablets have a length of approximately 18 mm, a width of approximately 9 mm, and a thickness of approximately 7 mm. The qualitative and quantitative composition of the DP, the respective functions of the components, and their quality standards are given in Table 15.

Table 15 Composition and Batch Formula of the Drug Product

(b) (4)

[redacted]

9. LABELING

[FDA will complete this section.]

USPI
Highlights: ***Adequate***

The Highlights section includes the proprietary name, established name, route of administration, and summary of dosage form and strength available:

TEPMETKO® (tepotinib) (b) (4) *tablets, for oral use* (b) (4)

COMMENT FOR LABELING: the proprietary name does not require (b) (4) *which should be removed in both instances of the highlights section. Dr. William Pierce concurs and included this change in the initial labeling review*

Section 2: ***Adequate***

Patients are instructed to swallow the tablets whole. "Do not chew, crush, or split tablets". This is consistent with developmental data such that no extemporaneous preparations were explored.

Section 3 Dosage Forms and Strengths: ***Adequate***

The available dosage form, strength, active ingredient equivalence statement, and description of the dosage form is all provided.

Section 11 Description: ***Adequate***
If the following excipients used in the drug product, include warning/declaration in the USPI:

- FD&C Yellow No.5 or No.6, as a color additive (21 CFR 201.20) is not used.
- Phenylalanine, as a component of aspartame (21 CFR 201.21) is not used.
- Sulfites (21 CFR 201.22) is not used.

The proprietary name, established name, dosage for, route of administration, salt equivalence statement, therapeutic class, qualitative composition, chemical/physical description of the drug substance is provided (structure, pKa, formula, molecular weight, and description)

Section 16 How Supplied/Storage and Handling: ***Adequate***

The available dosage form and strength is provided as well as the NDC number, identification markings for the tablet, description of the container closure (blisters in boxes), available units (30- and 60-count), and storage conditions.

*Manufacturer Information (Name and Address): **Provided: Adequate***

The distributor's information is provided:
EMD Serono, Inc.
Rockland, MA 02370
U.S.A.

Carton/Container Label ***Adequate***

Refer to Module 1 for images of the carton/container labels.

The secondary container (carton) includes the proprietary and established names, dosage strength, dosage form, route of administration, salt equivalence statement, "Rx only" statement, NDC number, lot number and expiration date, bar code, content, qualitative composition, distributor information, and statement that the container closure is child resistant.

The primary label (blister) includes the statement, "Keep out of reach of children", proprietary and established names, dosage form, strength, salt equivalence statement, distributor information, and bar code.

10. FINAL RISK ASSESSMENTS

[FDA will complete this section.]

SOLID ORAL

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium	XRPD in DS specs. Developmental data demonstrated the polymorphic form (b) (4) is maintained through drug product manufacturing and on storage. Stress conditions (light, heat, humidity, and freeze-thaw cycles) do not trigger polymorphic form changes in the drug product.	Low	
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Low		Low	
Moisture content	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Low		Low	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Dissolution – BCS Class II & IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	

11. RECOMMENDATION PAGE

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Kabir Shahjahan Date: October 28, 2020
Secondary Reviewer: Ali H. Al Hakim Date: October 28, 2020

Drug Product: Approval

Primary Reviewer: Olen Stephens Date: July 8, 2020
Secondary Reviewer: Anamitro Banerjee Date: August 19, 2020

Process and Facility: Approval

Primary Reviewer: Zhijin Chen Date: October 28, 2020
Secondary Reviewer: Bogdan Kurtyka Date: October 28, 2020

Biopharmaceutics: Approval

Primary Reviewer: Mei Ou Date: October 28, 2020
Secondary Reviewer: Banu Zolnik Date: October 28, 2020

Application Technical Lead: Approval

Xing Wang Date: November 3, 2020

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/

XING WANG
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