CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210238Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 210238
Review #1

Drug Name/Dosage Form	Avatrombopag Film-Coated Tablets
Strength	20 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	Eisai, Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	27-Sept-17	All
Amendment (SD 004)	27-Oct-17	Process
Amendment (SD 0011)	21-Dec-17	DP, Biopharm
Amendment (SD 0012)	05-Jan-18	Process
Amendment (SD 0016)	16-Jan-18	Biopharm
Amendment (SD 0021)	14-Feb-18	Biopharm
Amendment (SD 23)	16-Feb-18	DS
Amendment (SD 25)	20-Feb-18	DS

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gene Holbert	Charles Jewel
Drug Product	Paresma Patel	Anamitro Banerjee
Process	David Anderson	Ying Zhang
Microbiology	n/a	n/a
Facility	Wayne Seifert	Ruth Moore
Biopharmaceutics	Parnali Chatterjee	Okponanabofa Eradiri
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Rajiv Agarwal	Anamitro Banerjee

APPEARS THIS WAY ON ORIGINAL

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type IV			N/A	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76680	Original IND

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 210238 for Doptelet (Avatrombopag) Tablets, 20 mg. As part of this action, OPQ grants a (b)(4)-month re-test period for the drug substance when stored at (b)(4), and a 48-month drug product expiration period when stored at controlled room temperature (25°C/60% RH). There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant as a part of this recommendation.

II. Summary of Quality Assessments

A. Product Overview

NDA 210238 was submitted for Doptelet (Avatrombopag) Tablets, 20 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Avatrombopag is an orally bioavailable, small molecule thrombopoietin (TPO) receptor (c-Mpl) agonist that mimics the biologic effects of TPO indicated for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure. Avatrombopag is an NME which was originally investigated under IND 76680. .

Avatrombopag is a small achiral molecule that is manufactured (b)(4) The drug product, Doptelet (Avatrombopag) tablets, 20 mg, is presented as a (b)(4) yellow, film-coated round biconvex immediate-release tablet debossed with "AVA" on one side and "20" on the other. The drug product formulation includes avatrombopag maleate, lactose monohydrate, colloidal silicon dioxide, crospovidone (b)(4) magnesium stearate and (b)(4).

The dosing regimen for Doptelet (Avatrombopag) tablets is 40 or 60 mg orally once daily for 5 days. Per the dosing instructions, treatment with Doptelet (Avatrombopag) tablets should begin 10-13 days prior to the planned procedure.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 210238 and grants a (b)(4)-month re-test period for the drug substance and a 48 month expiration period for the drug product when stored at ICH controlled room temperature in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure
Duration of Treatment	Duration of treatment is 5 days

Maximum Daily Dose	60 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Avatrombopag maleate drug substance is a white to off-white, non-hygroscopic, powder that is practically insoluble in water and in 0.1 M HCl.

Avatrombopag maleate drug substance is an achiral molecule that is manufactured in (b) (4). Eisai Pharmaceutical India is responsible for the manufacture (b) (4) and Kashima Plant Eisai Co is responsible for the manufacture (b) (4) The drug substance manufacturing process is described in sufficient detail to clearly delineate how impurities are formed, how changes in the process could potentially affect the formation, fate, and purge of impurities and why the proposed control strategy is suitable for the drug substance manufacturing process. The drug substance was adequately characterized by UV, IR, NMR, MS, XRPD, TGA/DTA and elemental analysis. The drug substance was investigated for polymorphism and the data confirmed that avatrombopag exhibits polymorphic behavior. (b) (4) The drug substance reviewer is satisfied that the potential for polymorphism has been adequately addressed in this application.

The drug substance is stored (b) (4)

Specifications and acceptance criteria for the drug substance are consistent with ICH Q6A and are adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the drug product. All analytical methods are described in adequate detail and are appropriate for their intended use. All validation parameters - system suitability and system precision, specificity, linearity, range, precision, accuracy, ruggedness, robustness, and stability of solutions are provided in the NDA.

Batch analyses were included for seventeen drug substance batches. Eight batches were manufactured at (b) (4)

(b) (4) Details pertaining to batch numbers and use can be found in the drug substance review.

This application contained two types of stability studies: (1) formal stability studies (FSS) (long-term, accelerated and stress testing) and (2) bridging stability studies (BSS). The bridging stability studies were to ensure the equivalence of stability of avatrombopag maleate when the drug substance is stored (b) (4) This study was also conducted to ensure the equivalence of stability of drug substance produced (b) (4) The primary registration batches were manufactured at (b) (4). The stability data for the registration batches stored at (b) (4) (b) (4). Accordingly, the reviewer determined that microbial limits testing were not required for the drug substance. (b) (4)

The bridging study demonstrated no significant differences in any attribute tested and it was concluded (b) (4)

The applicant requested (b) (4)-month retest for drug substance. The provided stability data and stress testing supports the proposed retest of (b) (4) months for the drug substance when stored at or below (b) (4).

All risks associated with the manufacture and control of the drug substance have been adequately addressed and as such this application is recommended for approval from a drug substance perspective.

Drug Product

The Doptelet (Avatrombopag) tablets, 20 mg is an immediate release dosage form for oral administration. The drug product is presented as a 20 mg, round, biconvex, debossed yellow film-coated, with "AVA" on one side and "20" on the other. The drug product contains 23.6 mg avatrombopag maleate equivalent to 20 mg of avatrombopag free base, lactose monohydrate, colloidal silicon dioxide, crospovidone (b) (4) magnesium stearate and (b) (4) Yellow. The drug product formulation contains no novel excipient and all excipients (b) (4) are compendial, and are commonly used in solid oral dosage forms. All the excipients are present within the levels listed in the inactive ingredient database. The components of the film coating are all compendial and sufficient information was provided in the application to support the use of this excipient.

The drug product is manufactured, controlled, packaged and release tested by

Kawashima Plant, Eisai Co., Ltd of Japan at a commercial batch size of (b) (4) tablets. The drug product is packaged (b) (4) (b) (4)

The drug product specifications are consistent with ICH Q6A and together with the risk assessments provide adequate controls to ensure the quality of the drug product throughout the product expiry. The proposed specification and acceptance criteria for the drug product and the controls for impurities in the drug substance are adequate to ensure that the critical quality attributes (CQAs) of this product are well controlled.

In support of the proposed 48 month expiry, the applicant provided 36 months of long term stability data and 6 months accelerated data for three registration batches of the drug product. The registration batches were packaged (b) (4) The applicant provided comparability and composition data (b) (4). It was concluded that the proposed commercial container closure is equivalent to the container closure used in the registration stability studies. The applicant also provided stability data for the drug product stored in the bulk packaging.

The stability studies were executed in accordance with the ICH Q1A and Q1B. The available stability data shows consistency over time and the statistical analysis of the long term data to support the proposed expiry. Based on the 36 months of stability data included in this application, Eisai Inc. proposed and the FDA accepts the expiration dating period of **48 months** for the drug product when stored at stored at controlled room temperature (25°C/60% RH) (b) (4)

All risks associated with the manufacture and control of the drug product have been adequately addressed and as such this application is recommended for approval from a drug product perspective.

Process

The drug product is manufactured at batch size of approximately (b) (4) kg which corresponds to (b) (4) tablets. The drug product formulation does not include overages. The commercial manufacturing process consists (b) (4) (b) (4)

(b) (4)

The proposed process (b) (4) were described in sufficient detail and justified. The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The description of the manufacturing process (b) (4). The applicant proposed to omit microbial limits testing from release testing of batches and this proposal was deemed acceptable by the process reviewer. The application is recommended for approval from a manufacturing process perspective.

Biopharmaceutics

The acceptability of the proposed dissolution method, the proposed dissolution acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability, the bridging of clinical and the commercial formulations and the risks (b) (4) were assessed by the biopharm reviewer. The dissolution method employed a USP Apparatus II (Paddle) at 50 rpm in 900 mL of 0.05M phosphate buffer. The proposed dissolution method was deemed acceptable for batch release and stability testing. The originally proposed dissolution acceptance criterion was Q= (b) (4)% in (b) (4) minute. Safety and efficacy studies supported a dissolution acceptance criterion of Q= (b) (4)% in 45 minutes. Accordingly, the agency recommended and the sponsor accepted the new dissolution acceptance criteria (Q= (b) (4)% in 45) and updated the drug product specification accordingly. The Applicant provided adequate data to support the bridge between the clinical and commercial formulations and implemented appropriate control strategies to mitigate the risk (b) (4) in the proposed drug product All risks associated with biopharmaceutics have been adequately addressed and as such this application is recommended for approval from a biopharmaceutics perspective.

Facilities

(b) (4)

(b) (4)

Environmental Assessment

The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b).

The request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

Appended at the end of the drug product review.

Sherita McLamore

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

---------- **DOSAGE FORMS AND STRENGTHS** ----------
Tablet: 20 mg (3)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	X
Dosage form, route of administration	X
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	X

2. *Section 2 Dosage and Administration*

DOPTELET should be taken orally once daily for 5 consecutive days with food.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	N/A

3. *Section 3 Dosage Forms and Strengths*

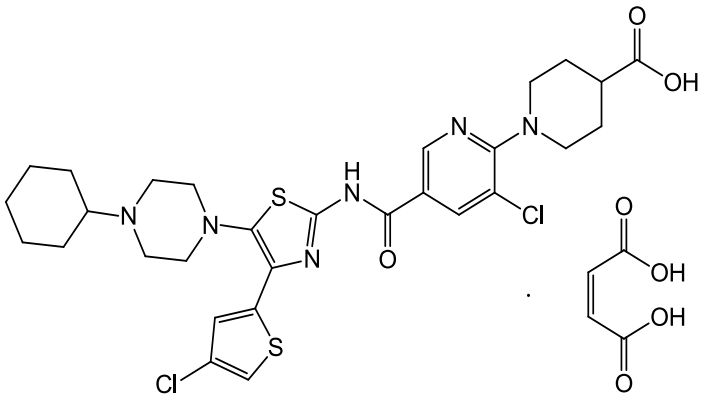
Tablets: (b) (4) 20 mg avatrombopag as (b) (4), round, biconvex, yellow, film-coated tablets (b) (4) debossed with "AVA" on one side and "20" on the other side.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	X
Strengths: in metric system	X
Active moiety expression of strength with equivalence statement (if applicable)	X
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	X

4. *Section 11 Description*

The active ingredient in DOPTELET is avatrombopag maleate, a thrombopoietin receptor agonist. The chemical name of avatrombopag maleate is 4-piperidinecarboxylic acid, 1-[3-chloro-5-[[[4-(4-chloro-2-thienyl)-5-(4-cyclohexyl-1-piperazinyl)-2-thiazolyl]amino]carbonyl]-2-pyridinyl]-, (2*Z*)-2-butenedioate (1:1). It has the molecular formula $C_{29}H_{34}Cl_2N_6O_3S_2 \cdot C_4H_4O_4$. The molecular weight is 765.73.

The structural formula is:



The aqueous solubility of avatrombopag maleate at various pH levels indicates that the drug substance is practically insoluble at pH 1 to 11.

DOPTELET is provided as an immediate-release tablet. Each DOPTELET tablet contains 20 mg avatrombopag (equivalent to 23.6 mg avatrombopag maleate) (b) (4) and the following inactive ingredients: lactose monohydrate, colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. Coating film: polyvinyl alcohol, talc, polyethylene glycol, titanium dioxide and ferric oxide yellow.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	X
Dosage form and route of administration	X
Active moiety expression of strength with equivalence statement (if applicable)	*Equivalency statement should be modified, the suggested edits above in red will be communicated to the applicant.*
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	N/A
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	X
Chemical name, structural formula, molecular weight	X
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	X

5. *Section 16 How Supplied/Storage and Handling*

DOPTELET 20 mg tablets are supplied as round, biconvex, yellow, film-coated tablets, and debossed with "AVA" on one side and "20" on the other side.

NDC 71369-020-10: carton with one blister card of ten 20 mg tablets
NDC 71369-020-15: carton with one blister card of fifteen 20 mg tablets

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store tablets in original package.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	
Available units (e.g., bottles of 100 tablets)	X
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	X
Special handling (e.g., protect from light)	*The applicant will be asked to include "store in original package" based on open dish photostability studies provided in the NDA.*
Storage conditions	X
Manufacturer/distributor name (21 CFR 201.1(h)(5))	X

Reviewer's Assessment of Package Insert: *Adequate.*
All sections of the prescribing information comply with all regulatory requirements. Minor edits are suggested for Section 3 (Dosage Forms and Strengths) based on an assessment by the clinical labeling team. The suggested edit to the equivalency statement provided in Section 11 (Description) is made to be consistent with the Guidance for Industry: "Naming of Drug Products Containing Salt Drug Substances."

The storage conditions have been revised to be consistent with USP controlled room temperature. The storage and handling revisions include a recommendation to store tablets in the original package based (b) (4) Refer to the Drug Product Review of this NDA for additional details on open dish studies.

The suggested equivalency statement and storage conditions revisions will be communicated to the applicant as part of the PI labeling comments.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	X	X
Dosage strength	X	X
Net contents	N/A	X
"Rx only" displayed prominently on the main panel	X	X
NDC number (21 CFR 207.35(b)(3)(i))	X	X
Lot number and expiration date (21 CFR 201.17)	X	X
Storage conditions		X
Bar code (21CFR 201.25)	X	X
Name of manufacturer/distributor	X	X
And others, if space is available		

Comment to the Applicant sent 04-Jan-2018 and Response Received 11-Jan-2018 (SD15):

- Revise the equivalency statement for the drug product carton labels to read: "Each tablet contains 20 mg avatrombopag (equivalent to 23.6 mg avatrombopag maleate)." We refer you to the Guidance for Industry: "Naming of Drug Products Containing Salt Drug Substances" found at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf.

Applicant Response: The applicant provided revised carton labels with the revised equivalency statement.
Evaluation: *Adequate.*

Comment to the Applicant sent 17-Jan-2018 and Response Received 24-Jan-2018 (SD20):

- Revise the storage conditions on carton labeling to read 'Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).' to be consistent with USP controlled room temperature.
- Include the statement 'Store tablets in original package.' as part of the storage conditions on the carton labeling based (b) (4) for your drug product.

Applicant Response: The applicant provided revised carton labels (copied above) with the revised stability conditions. The sponsor also included a statement providing the country of origin on the product packaging. The sponsor updated the NDA

stability sections in module 2.3.P.8 and module 3.2.P.8 to reflect the updated storage conditions:

"Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store tablets in original package."

Evaluation: The applicant provided updated carton labels, and the PI will be revised to be consistent with the label. The changes made from the original label are highlighted in red boxes on the carton labels copied above. The revised labels are adequate.

Adequate.

Reviewer's Assessment of Labels: *Adequate*

The carton and container labels meet all regulatory requirements. The applicant was sent an IR to revise the equivalency statement for the drug product carton labels to be consistent with the Guidance for Industry: "Naming of Drug Products Containing Salt Drug Substances." The applicant provided revised carton labels that are adequate.

The storage and handling temperature range was revised to be consistent with USP controlled room temperature. Additionally, the statement "Store tablets in original package" was added to the carton labels based (b) (4) Refer to the Drug Product Review of this NDA for additional details on open dish studies.

Overall Assessment and Recommendation: *Adequate.*

Primary Labeling Reviewer Name and Date:

Paresma Patel, Ph.D.
January 25, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, Ph.D.
January 25, 2018

Paresma Patel

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Anamitro Banerjee

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CHAPTER VII

BIOPHARMACEUTICS

NDA: 210238
Drug Product Name / Strength: Doptelet® (Avatrombopag) Tablets, 20 mg
Route of Administration: Oral
Applicant Name: Eisai Inc. (Eisai)

Background: Eisai Inc. is seeking approval for Doptelet® (Avatrombopag) Tablets, 20 mg to be administered orally for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a (b) (4) procedure *via* the 505 (b) (1) regulatory path.

The submission includes a number of avatrombopag formulations that were manufactured and subjected to clinical evaluation, (b) (4) The to-be-marketed (TBM) commercial image is the immediate-release, debossed, film-coated 2G tablet 'Formulation B' 20 mg strength containing 23.6 mg avatrombopag maleate. The Applicant conducted three pivotal safety and efficacy studies, E5501-J081-204, E5501-G000-310 and E5501-G000-311 with the TBM 2G tablet 'Formulation B' 20 mg, Lots P23003ZZA and P55026ZZA, in addition to a number of pharmacokinetic (PK) studies to assess the bioavailability of the TBM drug product. The recommended daily dose of the proposed drug product will be once daily to be taken orally with food for five (5) consecutive days based on the patient's platelet count prior to the initiation of a (b) (4) procedure.

REVIEW SUMMARY:
This Biopharmaceutics review evaluated the overall dissolution data supporting; **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criterion, **3)** the bridging of the formulations due to formulation changes, and **4**) the risk assessment (b) (4)

Based on the review of the provided information/data, Biopharmaceutics has the following recommendations:

1) ***Proposed Dissolution Method:*** The dissolution method for the proposed drug product was developed using USP Apparatus 2 at a paddle speed of 50 rpm in 900 mL of 0.05 M phosphate buffer, pH 6.8 containing 0.25% CTAB. The proposed dissolution method has the ability to detect certain changes in the formulation and manufacturing process and can reject batches (b) (4). The proposed dissolution method described below is acceptable for batch release and stability testing of the proposed drug product.

Parameters	Method
Apparatus/Speed	USP Apparatus 2 (paddle)/ 50 rpm
Media/Volume	0.25% w/v CTAB in 0.05 M phosphate buffer pH 6.8 /900 mL
Bath temperature	37.0±0.5°C
Analytical Method	UV_{Δ}/337 nm and 650 nm

2) ***Proposed Dissolution Acceptance Criterion***: The Applicant proposed the dissolution acceptance criterion of "Q=(b)(4)% in (b)(4) minutes" for batch release and stability testing of the proposed drug product. However, the dissolution data for the batches used in the pivotal safety and efficacy studies support the dissolution acceptance criterion of Q=(b)(4)% in 45 minutes for dissolution testing of the proposed drug product. In response to the IR comment, the Applicant accepted the FDA recommended dissolution acceptance criterion of Q=(b)(4)% in 45 minutes for batch release and stability testing of the proposed drug product. In addition the Applicant made a commitment to update the drug product specifications accordingly.

	Applicant Proposed Acceptance Criterion	FDA Recommended Acceptance Criterion
Dissolution Acceptance Criterion	Q=(b)(4)% in (b)(4) minutes	Q=(b)(4)% in 45 minutes

3) ***Bridging of the Formulations Due to Tablet Debossing:*** The Applicant provided adequate in vitro dissolution data to support the bridge between the tablet batches 'P23003ZZA' used in the pivotal safety and efficacy studies and the TBM commercial final image batch 19F1660601, which is debossed.

4) Biopharmaceutics Risk Assessment:

(b)(4) The Applicant provided solubility and dissolution data as well as control strategies to mitigate the risk (b)(4) in the proposed drug product. However, the solubility and dissolution data provided are limited, and the in vivo effects (b)(4) cannot be fully predicted based on the provided solubility and dissolution data. The Applicant will monitor (b)(4) the drug product at release and in the stability samples using XRPD. The CMC information related to the control strategy(ies) (b)(4) in the drug product will be reviewed by the CMC Reviewer(s).

- ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 210238 for avatrombopag tablets is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:
Parnali Chatterjee, PhD *02/08/2018*

Secondary Biopharmaceutics Reviewer Name and Date:
Okpo Eradiri, PhD 02/08/2018

BIOPHARMACEUTICS ASSESSMENT

➢ LIST OF SUBMISSIONS REVIEWED:

Submissions Reviewed	Reference ID
Original NDA Submission 210238 Dated 09/22/2017	\\cdsesub1\evsprod\nda210238\0000\m1\us\cover.pdf, SDN (1)
Response to Information Request (IR) Comments	
IR#1 Dated 12/11/2017	\\cdsesub1\evsprod\nda210238\0011\m1\us\1111-quality-info-amendment.pdf, SDN (12)
IR#2 Dated 01/04/2018	\\cdsesub1\evsprod\nda210238\0016\m1\us\1111-quality-info-amendment.pdf, SDN (17)
IR#3 Dated 02/05/2018	

➢ DRUG PRODUCT:

The proposed drug product is an immediate-release, biconvex, debossed, film-coated tablet intended for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a (b) (4) procedure. According to the Applicant, the recommended daily dose of avatrombopag will be once daily to be taken orally with food for five (5) consecutive days based on the patient's platelet count prior to the initiation of a (b) (4) procedure (see **Table I** below).

Table I. Recommended Daily Dose for Doptelet® (Avatrombopag) Film-Coated Tablets, 20 mg

Platelet Count ($x10^9$/L)	Once Daily Dose	Duration
<40	60 mg (3 X 20 mg)	5 days
≥40 to <50	40 mg (2 X 20 mg)	5 days

The Applicant developed a wide variety of formulations (b) (4) during the product development of avatrombopag. The 2G Formulation B was developed as 5 mg, 10 mg, 20 mg, and 40 mg strength products, however, the qualitative and quantitative compositions, and the manufacturing process for the different strengths are different. The various strengths of the 2G Formulation B were manufactured at Kawashima Industrial Park, Eisai Co., Ltd (see **Table II**). The 2G Formulation B batches, P23003ZZA and P55026ZZA, used in the pivotal safety and efficacy studies E5501-J081-204, E5501-G000-310, and E5501-G000-311 were manufactured at the Kawashima Industrial Park, Eisai Co., Ltd.

Table II. Manufacturing Site for the Various Strengths of the 2G Formulation B Drug Product

Manufacturing Site	Dosage Form Formulation	Dosage Strength	Batch Scale (tablet)	Drug Product Lot No.
Kawashima Industrial Park, Eisai Co., Ltd.	Film-coated tablet (Formulation B)	5 mg	(b) (4)	P01006ZZ
				P24001ZZ
		10 mg		P01007ZZ, P1Y013ZZ, P22003ZZ
		20 mg		P01008ZZ, P01009ZZ, P15005ZZ, P15006ZZ, P1X033ZZ, P1X034ZZ, P1X035ZZ, P1X036ZZ, P22006ZZ
				P23003ZZ, P24003ZZ, P3X001ZZ [a], P41001ZZ [a], P41002ZZ [a], P55026ZZ
		40 mg		P97001ZZ, P01010ZZ
		Placebo for 5 mg		P9Z009ZZ
		Placebo for 10 mg		P9Z010ZZ, P22001ZZ
		Placebo for 20 mg		P9Z011ZZ, P1X031ZZ, P22002ZZ
				P2Y002ZZ, P55025ZZ
		Placebo for 40 mg		P9Z012ZZ

According to the Applicant, the 2G Formulation B film-coated tablet, 20 mg, is the to-be-marketed (TBM) drug product or the commercial market image (CMI). The qualitative and quantitative composition of the proposed TBM product is given in **Table III**; the formulation contains lactose monohydrate, crospovidone (b) (4), colloidal silicone dioxide, microcrystalline cellulose, and magnesium stearate. Because, the drug substance exhibits poor powder flow properties, the TBM product was manufactured (b) (4)

Component	Amount (mg)	Function	Specification
Core Tablet			
Avatrombopag Maleate (equivalent to free form)	23.6 (20.0) [a]	Active Ingredient	In-house
Lactose Monohydrate	(b) (4)		NF / Ph. Eur.
Colloidal Silicon Dioxide [b]			NF / Ph. Eur.
Crospovidone (b) (4)			NF / Ph. Eur.
Magnesium Stearate			NF / Ph. Eur.
Microcrystalline Cellulose			NF / Ph. Eur.
Crospovidone (b) (4)			NF / Ph. Eur.
Magnesium Stearate			NF / Ph. Eur.
(b) (4)			-
Film Coat			
(b) (4)			In-house
			USP / Ph. Eur
			-

NF = National Formulary(U.S.), Ph. Eur. = European Pharmacopoeia, USP = United States Pharmacopeia
q.s. = *quantum sufficit.*
[a] Quantity of active moiety is determined on the basis of avatrombopag free form
(b) (4)

Table III. Qualitative and Quantitative Composition of the TBM Formulation B Film-coated Tablet, 20 mg

The 2G Formulation B was used in multiple clinical studies, including the Phase II clinical study E5501-J081-204 and pivotal safety and efficacy studies, E5501-G000-302, E5501-G000-305, E5501-G000-310, and E5501-G000-311 as shown in **Table IV**.

Table IV. Phase III Pivotal Clinical Studies Conducted with the TBM Formulation B Tablet Drug Product, 20 mg Strength

Study No.	Study Description	Dosage form	Dosage Strength	DP Lot No.	DS Lot No.
E5501-G000-302	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 Plus Standard Care for the Treatment of Thrombocytopenia in Adults with Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura)	Film-coated Tablet (Formulation B)	5 mg	P01006ZZ	4103.HP-002
			10 mg	P01007ZZ	4103.HP-002
			10 mg	P1Y013ZZ	DS11001
			10 mg	P22003ZZ	DS11001
			20 mg	P01008ZZ	4103.HP-002
			20 mg	P01009ZZ	4103.HP-002
			20 mg	P15005ZZ	4103.HP-002
			20 mg	P1X036ZZ	DS11002
			20 mg	P22006ZZ	DS11004
			Placebo for 5 mg	P9Z009ZZ	N/A
			Placebo for 10 mg	P9Z010ZZ	N/A
			Placebo for 10 mg	P22001ZZ	N/A
			Placebo for 20 mg	P9Z011ZZ	N/A
			Placebo for 20 mg	P1X031ZZ	N/A
			Placebo for 20 mg	P22002ZZ	N/A
E5501-G000-305	A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel-Group Trial with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 versus Eltrombopag, in Adults with Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenia Purpura)	Film-coated Tablet (Formulation B)	5 mg	P01006ZZ	4103.HP-002
			10 mg	P01007ZZ	4103.HP-002
			10 mg	P1Y013ZZ	DS11001
			20 mg	P01008ZZ	4103.HP-002
			20 mg	P01009ZZ	4103.HP-002
			20 mg	P15006ZZ	4103.HP-002
			20 mg	P1X033ZZ	DS11001
			20 mg	P1X034ZZ	DS11002
			20 mg	P1X035ZZ	DS11002
			20 mg	P1X036ZZ	DS11002
			Placebo for 5 mg	P9Z009ZZ	N/A
			Placebo for 10 mg	P9Z010ZZ	N/A
			Placebo for 20 mg	P9Z011ZZ	N/A
			Placebo for 20 mg	P1X031ZZ	N/A
E5501-G000-310	A Randomized, Global, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Once-daily Oral Avatrombopag for the Treatment of Adults with Thrombocytopenia Associated with Liver Disease Prior to an Elective Procedure	Film-coated Tablet (Formulation B)	20 mg	P23003ZZ	DSB11005
			20 mg	P55026ZZ	DS13003
			Placebo for 20 mg	P2Y002ZZ	N/A
			Placebo for 20 mg	P55025ZZ	N/A
E5501-G000-311	A Randomized, Global, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Once-daily Oral Avatrombopag for the Treatment of Adults with Thrombocytopenia Associated with Liver Disease Prior to an Elective Procedure	Film-coated Tablet (Formulation B)	20 mg	P23003ZZ	DSB11005
			20 mg	P55026ZZ	DS13003
			Placebo for 20 mg	P2Y002ZZ	N/A
			Placebo for 20 mg	P55025ZZ	N/A

N/A = not applicable.

(b) (4)

- ***BCS DESIGNATION***

Reviewer's Assessment: Not Applicable

The Applicant did not request an official BCS designation for the proposed TBM Formulation B drug product. The active ingredient in the proposed drug product is avatrombopag, which is non-hygroscopic, white to off-white crystalline powder (see **Figure 1**).

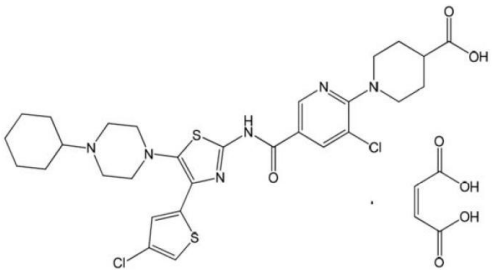

Figure I: Chemical structure of Avatrombopag 1-(3-chloro-5-{[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)-1,3-thiazol-2-yl]carbamoyl}pyridine-2-yl)piperdine-4-carboxylic acid

The molecular weight of the maleate salt of avatrombopag is 765.73 grams/mole, whereas the molecular weight of avatrombopag free base is 649.65 grams/mole. The drug substance exhibits three dissociation constants, with pKa=2.8 for the pyridine group, pKa=3.6 for the carboxylic acid group, and pKa=8.4 for the piperazine moiety. The maleate salt of the drug substance (b) (4)

- ***Solubility:***

In order to evaluate the aqueous solubility of avatrombopag maleate, the Applicant performed equilibrium solubility studies on avatrombopag maleate in Britton-Robinson buffered solutions of fixed ionic strength (*I*=0.3) in 0.1 mol/L hydrochloric acid and at varying pH range, 3-11 (see **Table V**).

Table V. Equilibrium Solubility Profile of Avatrombopag Maleate in Britton-Robinson Buffered Solutions of Fixed Ionic Strength (*I*=0.3) in Hydrochloric Acid and at Varying pH Range, 3-11

Test Media	Solubility (μg/mL)	Descriptive Terms in USP
0.1 mol/L Hydrochloric acid	5.8×10^{-1}	Practically insoluble
pH 3 Briton-Robinson buffer	6.5×10^{-3}	Practically insoluble
pH 5 Briton-Robinson buffer	3.8×10^{-2}	Practically insoluble
pH 7 Briton-Robinson buffer	2.7×10^{-2}	Practically insoluble
pH 9 Briton-Robinson buffer	1.3×10^{-1}	Practically insoluble
pH 11 Briton-Robinson buffer	3.4×10	Practically insoluble

Reviewer's Assessment *of Avatrombopag Maleate Solubility:* Avatrombopag maleate exhibits pH-dependent solubility profile, with highest solubility (~34 μg/mL) in pH 11 Britton-Robinson buffered solution and lowest solubility at pH 3 (~0.0065 μg/mL).

- ***Permeability:***

The current submission does not contain any information on the in vitro permeability profile of avatrombopag. However, the absorption of avatrombopag maleate can be summarized from

the Phase I single-dose ^{14}C-labeled mass balance study conducted in human volunteers with 24 mg suspension of avatrombopag (~20 mg as free base) spiked with 100 µCi ^{14}C-avatrombopag (Absorption, Distribution, Metabolism, and Excretion; ADME study 501-PK-901). According to the Applicant, approximately 88% of the administered radioactive dose was recovered from the feces, unchanged (see **Table VI**). The levels of radioactivity recovered from the urine were very low or undetectable. In plasma, majority of the administered radioactive dose was recovered unchanged. Following a single oral dose of 24 mg (~20 mg as free base) suspension of avatrombopag to human volunteers, the drug exhibited the following pharmacokinetic (PK) parameters: a Cmax of 218 ng/mL, a Tmax of 6 hours, and a terminal half-life of 24.5 hours.

Table VI. Pharmacokinetic (PK) Profile Following Single-oral Administration of 24 mg Suspension of Avatrombopag (~20 mg as free base) spiked with 100 µCi ^{14}C-Avatrombopag to Healthy Human Volunteers

Study No. (LLOQ)	Healthy Subjects No. M/F Age range (y)	Avatrombopag Treatment (N, Dose, Dosage Form, Route) [Product ID]	C_{max} (ng/mL)		t_{max} (h)[a]	$AUC_{(0-t)}$ (ng·h/mL)[b]		$AUC_{(0-inf)}$ (ng·h/mL)		$t_{½}$ (h)	Study Report Location
			Geo Mean (%CV)[c]	Arith Mean (SD)	Median (Min – Max)	Geo Mean (%CV)[c]	Arith Mean (SD)	Geo Mean (%CV)[c]	Arith Mean (SD)	Arith Mean (SD)	
Mass Balance Study											
501-PK-901 (2.07 ng eq/mL)	6 healthy males 22 – 45y	20-mg ^{14}C-avatrombopag suspension	218[g] (20.3)	222[h] (45.1)	6.0 (4.0 – 8.0)	6560[i] (25.3)	6740[i] (1710)	6750[i] (24.7)	6930[i] (1710)	24.5 (2.62)	Module 5, Section 5.3.3.1

***Reviewer's Assessment** of Avatrombopag Absorption:* Based on the information provided in the mass balance study, 501-PK-901, it can be concluded that avatrombopag is slowly absorbed with a Tmax of 6 hours with moderate-high absorption profile, and is slowly eliminated from the body with a terminal half-life of 24 hours. It should be noted that the Applicant indicated high inter- and intra-subject variability in the PK data following oral administration of avatrombopag from a suspension formulation under fasted conditions.

- ***DISSOLUTION INFORMATION:***

Because the proposed drug substance exhibits low aqueous solubility profile in physiological pH range of 1 to 9 (see **Table V**) (b) (4), dissolution testing will be a critical quality attribute (CQA) for the proposed drug product. The Applicant utilized dissolution testing throughout the proposed drug product development process across the different manufacturing processes for the batches used in the pivotal clinical PK studies and for batches on stability. The dissolution method was also used to aid in the selection of the final drug product formulation and final manufacturing process.

- ***PROPOSED DISSOLUTION METHOD:***

The Applicant proposed a dissolution method that would be sensitive to certain formulation and manufacturing process (b) (4) of the proposed drug product and would be a surrogate quality control tool for batch release and stability testing of the

finished drug product. The dissolution method proposed by the Applicant for the dissolution testing of Doptelet® (avatrombopag) tablets is shown in **Table VII.**

Table VII. Proposed Dissolution Method and Dissolution Acceptance Criterion for Doptelet® (Avatrombopag) Tablets, 20 mg

Parameters	Method
Apparatus/Speed	USP Apparatus 2 (paddle)/ 50 rpm
Media/Volume	0.25% w/v CTAB in 0.05 M phosphate buffer pH 6.8 /900 mL
Bath temperature	37.0±0.5°C
Sampling Time-points	5, 10, 15, 20, 30, 45, 60 minutes
Dissolution Acceptance Criterion	Q= (b) (4)% in (b) (4) minutes

1. Dissolution Apparatus and Medium Volume:

(b) (4)

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(b) (4)

Overall Reviewer's Assessment *of the Proposed Dissolution Method:*
The Applicant developed a dissolution method for the proposed drug product that has the ability to detect changes in the formulation and manufacturing process based on the information provided in the current submission. However, the proposed dissolution method is (b) (4) evaluated in the current submission (b) (4) From a Biopharmaceutics perspective, the proposed dissolution method is adequate for batch release and stability testing of Avatrobopag Tablets, 20 mg Strength. The analytical method (UV/Vis) associated with the proposed dissolution method will be evaluated by the CMC Reviewer.

- ***PROPOSED DISSOLUTION ACCEPTANCE CRITERION:***

The Applicant proposed the following dissolution acceptance criterion for batch release and stability testing of Avatrombopag Tablets, 20 mg strength.

Dissolution Acceptance Criterion	Q= (b) (4) % in (b) (4) minutes

Reviewer's Assessment *of the Proposed Dissolution Acceptance Criterion*:
A review of the individual dissolution data of 12 dosage units of the bio-batches P23003ZZA and P55026ZZA used in the pivotal safety and efficacy studies, E5501-J081-204, E5501-G000-310 and E5501-G000-311, (shown in **Table XI)** indicate that the dissolution data supports 'Q= (b) (4) % in 45 minutes' as the dissolution acceptance criterion**.** In addition, individual dissolution data for fifteen (15) batches that were used in various Phase II and Phase III studies safety, efficacy and pharmacokinetic (PK) studies support the dissolution acceptance criterion 'Q= (b) (4) % in 45 minutes' for batch release and stability testing of the proposed drug product as shown in **Appendix I**.

An Information Request was conveyed to the Applicant recommending the dissolution acceptance criterion 'Q= (b) (4) % in 45 minutes' for batch release and stability testing of the proposed drug product on 02/05/2018. In response to the IR comment, the Applicant accepted the FDA recommended dissolution acceptance criterion 'Q= (b) (4) % in 45 minutes' for the dissolution testing of the proposed drug product. In addition, the Applicant has made a commitment to update the product specification tables in the eCTD modules, 3.2.P.5.1 for Specification(s) and 2.3.P.5 for the Control of Drug Product, along with the sections 3.2.P.5.2.7 for Dissolution, 3.2.P.8.1 for Stability Summary and Conclusion, and 2.3.P.8 for Stability data.

Table XI. Dissolution Data for the Bio-Batches P23003ZZA and P55026ZZA Used in the Pivotal Safety and Efficacy Studies, E5501-J081-204, E5501-G000-310 and E5501-G000-311

Table 1.11.1-6 Individual Dissolution Rate for Lot No. P23003ZZ

min	5	10	15	20	30	45	60
Vessel 1							(b) (4)
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							
Vessel 7							
Vessel 8							
Vessel 9							
Vessel 10							
Vessel 11							
Vessel 12							
Avg	**33.4**	**64.0**	**77.9**	**85.2**	**91.8**	**95.7**	**97.3**
Max							(b) (4)
Min							
SD	**1.83**	**1.43**	**1.09**	**1.02**	**0.87**	**0.91**	**0.97**
RSD (%)	**5.47**	**2.23**	**1.40**	**1.20**	**0.94**	**0.96**	**1.00**

Data from Figure 3.2.P.5.6-1

Table 1.11.1-7 Individual Dissolution Rates for Lot No. P55026ZZ

min	5	10	15	20	30	45	60
Vessel 1							(b) (4)
Vessel 2							
Vessel 3							
Vessel 4							
Vessel 5							
Vessel 6							
Vessel 7							
Vessel 8							
Vessel 9							
Vessel 10							
Vessel 11							
Vessel 12							
Avg	**14.2**	**50.5**	**74.4**	**86.0**	**94.2**	**96.8**	**97.5**
Max							(b) (4)
Min							
SD	**1.15**	**1.93**	**1.25**	**1.38**	**1.48**	**1.66**	**1.53**
RSD (%)	**8.12**	**3.83**	**1.68**	**1.61**	**1.57**	**1.71**	**1.57**

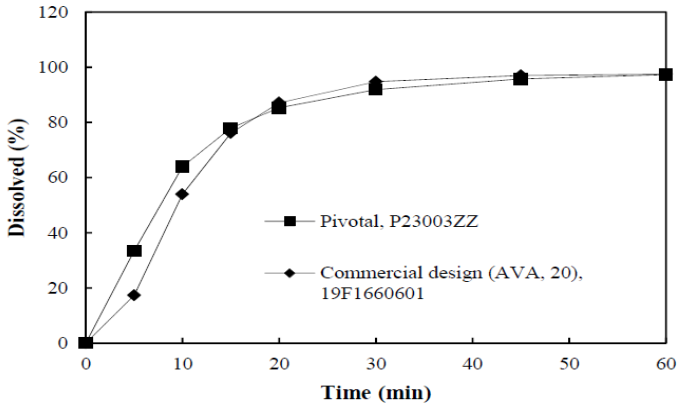
Data from Figure 3.2.P.5.6-1

- ***BRIDGING OF FORMULATIONS DUE TO TABLET SHAPE CHANGE:***

The 2G Formulation B tablet (batch P23003ZZ) used in the pivotal clinical studies was modified to form the TBM final commercial image, batch 19F1660601, by 'debossing'. In order to support the 'debossing' of the TBM drug product, the Applicant used the proposed dissolution method to generate dissolution profile (see **Figure X**) for batch P23003ZZ with

'undebossed' tablet and batch 19F1660601, with 'debossing'. The debossed tablet (batch 19F1660601) exhibits a slightly slower initial release of the avatrombopag up to 15 minutes as compared to the 'undebossed' tablet (batch P23003ZZ). However, after 20 minutes, the dissolution profile of the undebossed and debossed tablets are similar with >85% release of avatrombopag at 60 minutes, as shown in **Figure X**.

Figure X. Mean Dissolution Profile for Undebossed Batch P23003ZZ and TBM Drug Product Batch 19F1660601 with Debossing



Reviewer's Assessment for *Bridging Tablets with Different Shape*: The Applicant provided in vitro dissolution profile to support the 'debossing' of the TBM final commercial image. From **Figure X**, it can be seen that the modification to the tablet shape from 'undebossed' to 'debossed' did not change the dissolution profile between the batch P23003ZZ of the drug product and the batch 19F1660601, which is TBM final commercial drug product.

- ***BIOPHARMACEUTICS RISK ASSESSMENT:***

According to the Applicant, (b) (4) (b) (4) (b) (4) However, the Applicant provided dissolution profile data for drug products manufactured (b) (4)

Though the Applicant provided solubility and dissolution data as well as control strategies to mitigate the risk (b) (4) in the proposed drug product, there is limited information, (b) (4) The Applicant has made a

commitment to monitor (b) (4) the drug product at release and in the stability samples using XRPD. These control stategies (b) (4) in the drug product should be discussed in the CMC chapters.

- ***POST-APPROVAL COMMITMENTS:*** **None**

- ***LIST OF DEFICIENCIES:*** **None**

- ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 210238 for is recommended for **APPROVAL**.

- ***SIGNATURES***

Primary Biopharmaceutics Reviewer Name and Date:

Parnali Chatterjee, PhD ***02/08/2018***

Secondary Reviewer Name and Date:

Okpo Eradiri, PhD 02/08/2018

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APPENDIX II

IR#1. List of Biopharmaceutics Information Request Comments Dated 12/11/2017

1. Provide complete dissolution profile data (individual, means, ranges, %CV) across all time-points for (1) the 2G Formulation B, 20 mg strength drug product used for the dissolution method development, and (2) the bio-batches P23003ZZA and P55026ZZA that were used in the pivotal Phase III clinical studies E5501-G000-310 and E5501-G000-311.

2. Please confirm if the free base was taken into consideration in the calculation for the cumulative percent (%) drug released from the 2G Formulation B, 20 mg strength drug product.

If you have provided the above requested information/data in the NDA submission, please point out the specific location(s) in eCTD where the dissolution data are located.

The Applicant responded to the Information Request Comment on 12/21/2017
(refer to: \\cdsesub1\evsprod\nda210238\0011\m1\us\1111-quality-info-amendment.pdf)

Reviewer's Assessment of IR#1:
The Applicant provided dissolution data for selected dissolution profiles, therefore, the Applicant will be requested to provide dissolution data for parameters evaluated for the dissolution method development.

IR#2. List of Biopharmaceutics Information Request Comments Dated 01/04/2018

1. We have reviewed the dissolution profile data provided in response to the Information Request dated Dec 11, 2017. However, we noticed that selected dissolution data were provided for the 2G Formulation B, 20 mg strength drug product used for the dissolution method development. We request that you provide dissolution profile data (means, %CV) across all time-points for Figures 3.2.P.2.2-1, 3.2.P.2.2-2, 3.2.P.2.2-4, 3.2.P.2.2-5, and 3.2.P.2.1-2 as provided in the Module 3.2.P.2.2 in the eCTD. In addition, provide dissolution profile data (means, %CV) across all time-points for all 15 batches of Formulation B, 20 mg as depicted in Figure 3.2.P.5.6-1.

The Applicant responded to the Information Request Comment on 01/16/2018
(refer to: \\cdsesub1\evsprod\nda210238\0016\m1\us\1111-quality-info-amendment.pdf)

Reviewer's Assessment of IR#2:
The Applicant provided dissolution data for the requested dissolution profiles. Therefore the Applicant adequately addressed the Information Request.

IR#3. List of Biopharmaceutics Information Request Comments Dated 02/05/2018

1. The dissolution profile data for the 15 batches of Formulation B, 20 mg, support a dissolution acceptance criterion of "Q= (b)(4)% in 45 minutes" for batch release and stability testing of the proposed drug product. We recommend that you implement a dissolution acceptance criterion of "Q= (b)(4)% in 45 minutes'' for Doptelet® (Avatrombopag) Tablets, 20 mg. Note that setting of the dissolution acceptance criterion is based on S_2 testing (n=12) and therefore sometimes Stage 2 testing and occasional Stage 3 testing maybe needed.

2. Provide a copy of the updated specifications table of the drug product with the revised acceptance criterion for the dissolution test, and update other sections of the NDA, as appropriate.

The Applicant responded to the Information Request Comment on 02/07/2018

From: Stacie_OSullivan@eisai.com [mailto:Stacie_OSullivan@eisai.com]
Sent: Wednesday, February 07, 2018 2:46 PM
To: Haider, Rabiya <Rabiya.Haider@fda.hhs.gov>
Cc: Miller, Kelly <Kelly.Miller@fda.hhs.gov>; Lee, Wan <Wan.Lee@fda.hhs.gov>
Subject: Re: FDA Information Request NDA 210238 Doptelet (avatrombopag) - Please Respond by February 7, 2018

Dear Dr. Haider,

Please see our response to this Information Request below:

1. Eisai commits to implement a dissolution acceptance criterion of "Q= (b)(4) in 45 minutes'' for release of Doptelet (avatrombopag) tablets, 20 mg.

2. Eisai will update the specification tables as provided in 3.2.P.5.1 Specification(s) and 2.3.P.5 Control of Drug Product. Other eCTD sections to be modified as appropriate to this change are 3.2.P.5.2.7 Dissolution, 3.2.P.8.1 Stability Summary and Conclusion and 2.3.P.8 Stability. These five sections will be updated in a forthcoming formal amendment of the NDA.

Please let me know if you have any questions.

Kind regards,
Stacie

Stacie P. O'Sullivan
Assoc. Director, Regulatory Affairs
Eisai Inc.
6611 Tributary Street
Baltimore, MD 21224

Office: 410-631-8138
Cell: (b) (6)

Reviewer's Assessment of IR#3:

In response to the IR Comment#3, the Applicant implemented the FDA recommended dissolution acceptance criterion for the dissolution testing of the proposed drug product. In addition, the Applicant has made a commitment to update product specification in the eCTD modules and the stability specifications in a future amendment. Therefore the Applicant adequately addressed the Information Request.

Parnali Chatterjee

Digitally signed by Parnali Chatterjee
Date: 2/08/2018 02:12:40PM
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Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 2/08/2018 01:40:44PM
GUID: 50bdfe8d00003559ede66be3fd299f65

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 210238 Avatrombopag 20 mg Film-Coated Tablets

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, stability At release and stability)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Physical Stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Content Uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Justification is provided, refer to OPF review.
Dissolution – BCS Class II & IV	• Formulation • Raw Materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval, refer to BioPharm review.

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 3/01/2018 11:59:40AM
GUID: 503257950000415755492db5bb8b1a5c

DRUG PRODUCT (Memo)

Product Background:

NDA/ANDA (review cycle number): 210238 (Review 1)

Drug Product Name / Strength: Avatrombopag film-coated tablets, 20 mg

Route of Administration: Oral administration

Indication: Treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure.

Maximum Recommended Daily Dose: 60 mg, once daily

Applicant Name: Eisai Inc.

Review Recommendation: **Adequate**
The drug product avatrombopag film-coated tablet, 20 mg is recommended for approval from the perspective of the drug product reviewer in the Office of New Drug Products, Office of Pharmaceutical Quality.

Review Summary: This is an addendum to the drug product review for avatrombopag tablets that was submitted in Panorama by Paresma Patel on 09-Jan-2018. This review provides a revised specifications table with updates to the dissolution specifications. The revisions were submitted in SD 22 as a response to biopharmaceutics information request. The revised specifications are adequate from the perspective of the drug product reviewer. The drug product avatrombopag 20 mg film coated tablet is recommended for *approval* from the drug product perspective.

List Submissions being reviewed (table): NDA 201238, SD22 (IR response)

Concise Description Outstanding Issues Remaining: N/A

P.5 Control of Drug Product

Table 1-3.2.P.5.1 Drug Product Specifications (14-Feb-2018)

Table 3.2.P.5.1-1 Specification for Avatrombopag Film-Coated Tablets, 20 mg

Test Item		Acceptance Criteria	Method Section Reference
Description		(b) (4) yellow, round biconvex, film-coated tablet, debossed, "AVA" on one side, and "20" on the other	Visual inspection (3.2.P.5.2.1)
Identification		A or B is selected	
A	1) UV/Vis 2) HPLC	1) λ_{max}: (b) (4) nm 2) The retention time should conform to that of the reference standard.	1) UV/Vis (3.2.P.5.2.2) 2) HPLC (3.2.P.5.2.3)
B	HPLC-PDA	The retention time should conform to that of the reference standard. The PDA-UV spectrum should conform to that of the reference standard.	HPLC-PDA (3.2.P.5.2.4)
Assay		(b) (4) of the label claim	HPLC (3.2.P.5.2.6)
Related substances		(b) (4) Others (Individual): (b) (4) Total:	HPLC (3.2.P.5.2.5)
Dissolution		Not less than (b) (4) (Q) in 45 minutes	USP <711>, Ph. Eur.2.9.3 and JP 6.10, Apparatus 2 UV/Vis (3.2.P.5.2.7)
Uniformity of dosage units (content uniformity)		Meets the requirements of JP 6.02, Ph. Eur. 2.9.40 and USP <905>	USP <905>, Ph. Eur. 2.9.40 and JP 6.02, UV/Vis (3.2.P.5.2.8)
Microbial limits		Microbial enumeration tests Total aerobic microbial count: (b) (4) CFU/g Total combined yeasts/molds count: CFU/g Tests for specified microorganisms Absence of *Escherichia coli* Absence of *Pseudomonas aeruginosa* Absence of *Staphylococcus aureus*	USP <61>, <62>, Ph. Eur. 2.6.12, 2.6.13 and JP 4.05, (3.2.P.5.2.9)

UV/Vis: UV-visible spectrophotometry
PDA: Photodiode Array

The acceptance criteria for dissolution have been tightened from Q= (b) (4) % in (b) (4) min to Q= (b) (4) % in 45 minutes based on an evaluation by the biopharmaceutics reviewer. Refer to the biopharmaceutics review in Panorama submitted by Parnali Chatterjee. All other specifications and acceptance criteria have remained the same.

The applicant provides updated analytical procedures and stability summary sections of the NDA reflecting the current dissolution specifications.

Reviewer's Assessment: *Adequate*
The revised dissolution specifications are adequate from the perspective of the drug product reviewer for the proposed 20 mg avatrombopag film coated tablets.

Primary Drug Product Reviewer Name and Date:
Paresma Patel, Ph.D.
February 16, 2018
Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Anamitro Banerjee, Ph.D.
February 16, 2018

Paresma Patel

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Date: 2/16/2018 03:05:58PM
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Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 2/16/2018 03:13:09PM
GUID: 5075764700003844b7bc89632228509f

U.S. FOOD & DRUG ADMINISTRATION

METHOD VERIFICATION
MATERIALS RECEIVED

NDA 210238

January 17, 2018

Stacie P. O'Sullivan
Associate Director Global Regulatory Strategy
Stacie_osullivan@eisai.com
Eisai Inc.
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms O'Sullivan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Doptelet ® (avatrombopag) 20 mg tablet and to our November, 29, 2017 letter requesting sample materials for method verification testing.

We acknowledge receipt on January 17, 2018, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3811) or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

Michael E. Hadwiger -S

Digitally signed by Michael E. Hadwiger -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300384000, cn=Michael E. Hadwiger -S
Date: 2018.01.17 14:44:06 -06'00'

Michael E. Hadwiger, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research