

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204886Orig1s000

CHEMISTRY REVIEW(S)

Zontivity (vorapaxar) tablets

NDA 204886

Summary Basis for Recommended Action from Chemistry, Manufacturing, and Controls

- Applicant:** Merck Sharp & Dohme Corp.
One Merck Drive
P.O. Box 100
Whitehouse Station
NJ 08889
- Indication:** For the reduction of atherothrombotic events in patients with a history of MI.
- Presentation:** The product will be available as single 2.08 mg strength tablets. The tablets are yellow colored, oval tablets debossed with Merck logo on one side and the product code ID “351” on the other side. The tablets are packaged in HDPE bottles with either 30-count or 90-count in each bottle. The tablets are also available in aluminum foil/foil blister unit dose packages of 100 count cartons (10 blisters with 10 tablets in each blister).
- EER Status:** Overall recommendation is “Acceptable” as of 5-Sep-2013.
- Consults:** ONDQA Biopharmaceutics - Acceptable (Okponanabofa Eradiri, 9-Jan-2014).

Microbiology - Acceptable (Erica Pfeiler, 7-Jun-2013)

Methods Validation - Acceptable (Wei Ye, 14-Nov-13)

EA – Categorical exclusion granted.
- Post-Approval Agreements:** None

Drug Substance:

The drug substance, vorapaxar sulfate, a new molecular entity, is a tricyclic himbacine derived selective inhibitor of platelet aggregation mediated by PAR-1. The drug substance is a white to off-white powder. The molecule contains seven chiral centers and a trans double bond. [REDACTED] (b) (4)

The drug substance quality is ensured through quality control of all starting materials, in-process controls throughout the manufacturing process, appropriate quality control of the isolated intermediates and the appropriate final drug substance specification. The drug substance acceptance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., description, identification, assay, impurities, particle size distribution, residual solvents, and heavy metals. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period of [REDACTED] (b) (4) when stored under controlled room temperature.

Drug product:

Zontivity (vorapaxar) tablets are an immediate release product to be marketed in single 2.08 mg strength. Each tablet contains 2.5 mg of vorapaxar sulfate which is equivalent to 2.08 mg of vorapaxar base. The drug product formulation uses standard compendial excipients, e.g., lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, and magnesium stearate. Additionally, the film coating contains lactose monohydrate, hypromellose, titanium dioxide, triacetin (glycerol triacetate), and iron oxide yellow. The manufacturing process [REDACTED] (b) (4)

[REDACTED] The manufacturing process has appropriate in-process controls to ensure the quality of the drug product. The product quality is further ensured through end product testing. The end product specification includes testing for description, identification, assay, uniformity of dosage units, degradation products, dissolution, and free base content determination. All analytical procedures for the drug product are adequately described and validated. The provided stability data support the proposed 24-month expiration period for this product.

The drug product is stored at 25°C with excursions permitted 15-30°C (59-86°F).

Conclusion: Adequate from CMC perspective.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: The application is recommended for “**Approval**” from CMC perspective.

Ramesh K. Sood, Ph.D.
Acting Director, DPA I/ONDQA

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/s/

RAMESH K SOOD
01/29/2014

NDA 204-886

ZontivityTM (Vorapaxar) Tablets, 2.08 mg

Merck Sharp & Dohme Corp

Thomas M. Wong, Ph.D.

Division of New Drug Quality Assessment I

Office of New Drug Quality Assessment

Division of Cardiovascular and Renal Products

Review of Chemistry, Manufacturing, and Controls

Table of Contents

The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature: See DARRTS	8
B. Endorsement Block: See DARRTS	8
C. CC Block See DARRTS	8
Chemistry Assessment.....	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	9
S DRUG SUBSTANCE.....	9
P DRUG PRODUCT	87
A APPENDICES	178
R REGIONAL INFORMATION	178
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	179
A. Labeling & Package Insert (Amendment #0030 dated 8/9/13)	179
B. Environmental Assessment Or Claim Of Categorical Exclusion	184
List Of Deficiencies To Be Communicated.....	184

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA: 204-886
2. REVIEW #: 1
3. REVIEW DATE: 9-Jan-14
4. REVIEWER: Thomas M Wong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

IND 71384

Document Type

Commercial IND

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original submission
Amendment # 0030
Amendment # 0033
Amendment # 0052
Amendment # 0058
Amendment # 0075
Amendment # 0077

Document Date

May 10, 2013
Aug 9, 2013
Sep 9, 2013
Nov 7, 2013
Nov 18, 2013
Dec 24, 2013
Dec 26, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Merck Sharp & Dohme Corp.

Address: One Merck Drive
P.O. Box 100
Whitehouse Station NJ 08889

Representative: Zak Huang, M.D.
351 North Sunnyside Pike, UG2CD-48
P.O. Box 1000
North Wales, PA 19454-2505

Telephone: (267) 305-6682

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zontivity
- b) Non-Proprietary Name (USAN): Vorapaxar sulfate
- c) Code Name/# (ONDC only): SCH 530348 (MK-5348), SCH 530348 sulfate, (SCH 530348 bisulfate, TRA bisulfate)
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Reduction of atherothrombotic events in patients with a history of MI.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 2.08 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN: Vorapaxar sulfate

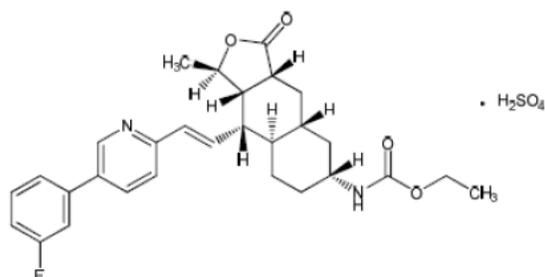
CAS Name: *N*-[(1*R*,3*aR*,4*aR*,6*R*,8*aR*,9*S*,9*aS*)-9-[(1*E*)-2-[5-(3-Fluorophenyl)-2-pyridinyl]ethenyl]dodecahydro-1-methyl-3-oxonaphtho[2,3-*c*]furan-6-yl]carbamic acid ethyl ester sulfate (1:1)

CAS registry number: 705260-08-8

Molecular formula: $C_{29}H_{33}FN_2O_4 \cdot H_2SO_4$

Structure

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 71,384	Commercial IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	Sep 5, 2013	Office of Compliance
Pharm/Tox	N/A		
Biopharm			
LNC	N/A		
Methods Validation	Acceptable	Nov 14, 2013	Dr. Wei Ye
DMFPA	N/A		
EA	Acceptable	Jan 9, 2014	Dr. Thomas Wong
Microbiology	Acceptable	Jun 7, 2013	Dr. Erika Pfeiler

Executive Summary Section

The Chemistry Review for NDA 204-410

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From the CMC perspective NDA 204886 for Zontivity™ (vorapaxar) Tablets is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)****Drug Product**

The applicant has developed an immediate release yellow colored oval tablet for oral administration. Each tablet is debossed with the Merck logo on one side and the product code ID "351" on the other side. The trade name for vorapaxar sulfate tablets is Zontivity™. Each tablet contains 2.08 mg of vorapaxar equivalent to 2.5 mg of vorapaxar sulphate and the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: lactose monohydrate, hypromellose, titanium dioxide, triacetin (glycerol triacetate), and iron oxide yellow. During manufacture and storage, partial conversion from vorapaxar sulfate to vorapaxar free base may occur. The tablets will be manufactured in MSD International GmbH located in Singapore with proposed commercial batch size of (b) (4)

Tablets are packaged in HDPE bottles with either 30-count or 90-count tablets per bottle; and in aluminum foil/foil blister unit dose packages of 100 tablets (one carton containing 10 of 10-count blister cards). Tablets are stored at 25°C (68 - 77°F), excursions permitted between 15 - 30°C (between 59 - 86°F). Available 12 months stability data support the proposed shelf life of 24 months when packaged in the proposed commercial packages and stored in the afore-mentioned storage conditions.

Drug Substance

Vorapaxar is a tricyclic himbacine-derived selective inhibitor of platelet aggregation mediated by PAR-1. It is a small molecule with molecular formula $C_{29}H_{33}FN_2O_4 \cdot H_2SO_4$ and molecular weight 590.7. It is a white to off-white powder with the highest solubility of 3.76 mg/mL in aqueous solution at pH 1.0 or in simulated gastric fluids at pH 1. The molecule contains seven chiral centers and a trans double bond. (b) (4)

. The drug substance is manufactured at Schering-Plough

Executive Summary Section

(Avondale) Company, in Ireland. The commercial batch size is currently based on (b) (4)

The applicant provided adequate information regarding structure elucidation and confirmation and impurity profile. Available 48 months stability data supports the proposed retest period of (b) (4) for the drug substance stored at (b) (4)

B. Description of How the Drug Product is Intended to be Used

The recommended dose is 2.08 mg of vorapaxar orally once daily, with or without food.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. From the CMC perspective NDA 204886 for Zontivity™ Tablets can be approved pending the biopharmaceutics reviewer's acceptance on the dissolution specification.

III. Administrative

A. Reviewer's Signature: See DARRTS

B. Endorsement Block: See DARRTS

C. CC Block See DARRTS

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/s/

THOMAS M WONG
01/09/2014

OLEN M STEPHENS
01/09/2014

CMC recommendation is for approval pending biopharmaceutics acceptance of dissolution specification

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 204886/000	Sponsor:	MERCK SHARP DOHME
Orig. Code:	110		126 EAST LINCOLN AVE RY 33 204
Priority:	1		RAHWAY, NJ 070650900
Stamp Date:	10-MAY-2013	Brand Name:	VORAPAXAR SULFATE
PDUFA Date:	10-MAY-2014	Estab. Name:	
Action Goal:		Generic Name:	VORAPAXAR SULFATE
District Goal:	10-DEC-2013	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET; VORAPAXAR SULFATE; 2.5MG

FDA Contacts:	T. WONG	Prod Qual Reviewer	(HFD-810)	3017961608
	Y. KNIGHT	Product Quality PM		3017962133
	A. BLAUS	Regulatory Project Mgr	(HFD-110)	3017961138
	K. SRINIVASACHAR	Team Leader		3017961760

Overall Recommendation:	ACCEPTABLE	on 05-SEP-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 04-JUN-2013	by EES_PROD		
	PENDING	on 04-JUN-2013	by EES_PROD		

Establishment:	CFN: 1036761	FEI: 1036761	
	MERCK SHARP & DOHME, WILSON FACILITY		
	WILSON, , UNITED STATES 278939613		
F No:		AADA:	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	05-SEP-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN: 0000000	FEI: 3004199021	
	MSD INTERNATIONAL GMBH (SINGAPORE BRANCH) 70 TUAS WEST DRIVE		
	SINGAPORE, , SINGAPORE		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	TABLETS, PROMPT RELEASE	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	13-JUN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9612726 FEI: 1000288672
SCHERING PLOUGH (AVONDALE)
LARAGH ROAD
AVONDALE, COUNTY WICKLOW, RATHDRUM, IRELAND

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JUN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9611641 FEI: 3003974846
SCHERING PLOUGH LABO NV
INDUSTRIEPARK 30 3100
HEIST-OP-DEN-BERG, ANTWERPEN, BELGIUM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-JUN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 2650155 FEI: 2650155
SCHERING-PLOUGH PRODUCTS, LLC
LAS PIEDRAS, , UNITED STATES 00771

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

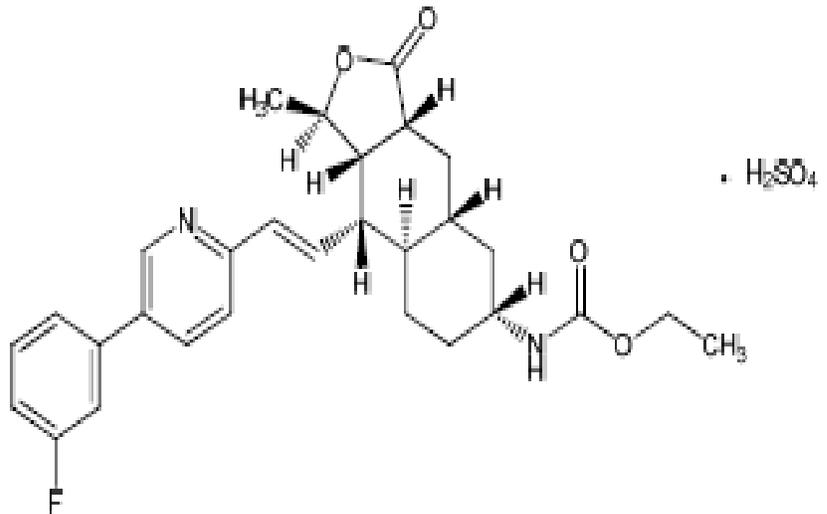
Milestone Date: 16-JUL-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Initial Quality Assessment
Branch I

OND Division: Division of Cardiovascular and Renal Products
NDA: 204886
Applicant: Merck Sharp & Dohme
Letter Date: May 10, 2013
Stamp Date: May 10, 2013
PDUFA Date: May 10, 2014
Tradename: Zontivity (Proposed)
Established Name: Vorapaxar Sulfate
Dosage Form: Tablets, 2.5 mg
Route of Administration: Oral
Indication: Reduction of atherothrombotic events in patients with a history of myocardial infarction
Assessed by: Kasturi Srinivasachar
ONDQA Fileability: Yes



Summary

This is an e-CTD 505(b)(1) NME NDA under the PDUFA V Program for vorapaxar sulfate film coated tablets, 2.5 mg. Vorapaxar is claimed to be a first-in-class selective antagonist of the protease-activated receptor-1 (PAR-1). Vorapaxar is said to block thrombin-mediated platelet aggregation and hence has the potential of reducing the risk of atherothrombotic complications of coronary disease. Clinical development of this drug was carried out under IND 71,384. An EOP2 CMC specific meeting was held with Schering (the original Sponsor) on Aug. 29, 2007 to discuss the designation of starting materials for the synthesis of vorapaxar sulfate, the product registration stability program and biopharmaceutic issues. Subsequently, a type C meeting was held with Merck on April 21, 2010 to discuss the ramifications from both clinical and quality perspectives of the newly discovered salt to free base conversion in the tablets being administered in the Phase 3 trials. The main outcome of this meeting was agreement by Merck to conduct BE studies with batches containing various levels of salt to free base conversion to ensure that a consistent product was administered during the Phase 3 trials. The Applicant states that the control strategies for vorapaxar drug substance and drug product are traditional and do not contain flexible regulatory approaches, design spaces, RTRT or PAT. However, QbD principles have been used in the development of the drug substance and drug product manufacturing processes.

Drug Substance

Vorapaxar sulfate is a white to off-white crystalline powder which contains 7 chiral centers and a trans double bond. Single crystal X-Ray diffraction confirms the assigned stereochemistry as well as the trans configuration of the double bond. (b) (4)

It exhibits pH dependent aqueous solubility – insoluble above pH 3 and highest solubility at pH 1 or in simulated gastric fluid at pH 1.4. (b) (4)

The manufacturing process has evolved during preclinical and clinical development and details are provided for the (b) (4)

All process parameters used in the manufacturing process have been evaluated for their variability and potential impact on the CQAs of the intermediates and drug substance. (b) (4)

Proven and acceptable ranges were established for the critical process parameters using DoE or OVAT studies. Controls have been

established for the (b) (4)

The NDA contains a discussion of impurities, including potential stereoisomeric impurities and potential genotoxic impurities. The origin and fate of impurities i.e. the potential to carry forward to the drug substance is also described. (b) (4)

The vorapaxar free base and final drug substance were also evaluated for these impurities and it was concluded that vorapaxar sulfate impurities are not genotoxic and can be controlled as ordinary impurities in accordance with ICH Q3A. The drug substance specification includes an ID test for the (b) (4) in addition to a test for vorapaxar. Two impurities listed are above the ICH qualification threshold of 0.15%. A particle size acceptance criteria of (b) (4) has been proposed. Batch analysis data have been submitted for batches used in clinical, safety and stability studies.

Stability of the drug substance has been monitored on 3 formal stability batches and one supportive batch at standard long term and accelerated conditions. Both the formal and supportive batches were manufactured at the intended commercial manufacturing site using the proposed commercial process (b) (4) The difference between the supportive and formal batches is that the (b) (4)

Based on the results of these studies, a retest date of (b) (4) is proposed for storage of the drug substance at controlled (b) (4)

Drug Product

Vorapaxar sulfate immediate release tablets will be marketed in a single strength of 2.5 mg for once daily use. Standard compendial excipients are used in the manufacture of the drug product. The sulfate salt was chosen for development in preference to the free base or other available salts because it was found to exist in a single, stable, crystalline form with no known polymorphs. Development of the product started with (b) (4) for Phase I studies (b) (4)

. For Phase II clinical trials a number of strengths of a tablet dosage form were developed and one of these, 2.5 mg was selected for Phase III studies. (b) (4) The intended commercial formulation is the same as the Phase III tablet except (b) (4)

The tablet shape is also different, oval versus round. These differences do not result in different dissolution behavior as shown by dissolution profile comparison in three media (0.1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8). The manufacturing process consists of the following unit operations: (b) (4)

Process development studies were conducted at the intended commercial scale of (b) (4) for process inputs that were deemed scale dependent. A risk based approach was used to identify process inputs to be evaluated during commercial manufacturing process development. This provided linkages between process inputs (raw material attributes and process parameters) for each of the process steps to in-process material attributes (blend uniformity, granule size distribution etc.) and drug product quality attributes such as assay, content uniformity, degradation products, moisture and dissolution. These studies were performed at scales up to (b) (4)

(b) (4), the intended commercial scale and assessed unit operations through single and multi-factor studies. From these studies preliminary proven acceptable process ranges for the unit operations could be identified. These preliminary proven acceptable ranges were further developed in (b) (4) process robustness studies which were designed as multi-factor studies to assess the potential for interactions between process parameters from one unit operation to another. Finally these ranges were confirmed in process robustness studies carried out at (b) (4). The knowledge gained during the development of the PARs was used to reassess the risks initially identified and the conclusion was that the existing controls are adequate to mitigate the risks.

Late in the development of the manufacturing process, after the process characterization and robustness studies were completed, conversion of the drug substance to its amorphous free base form was observed in vorapaxar tablets. This 'discovery' was actually triggered by the availability of information in the public domain about a similar conversion and its consequence in Effient (prasugrel tablets, NDA 22307). Considerable efforts have been devoted by the Applicant to understand this conversion and its ramifications.

Free base levels were retrospectively analyzed in Phase III batches and estimated to be within the range of (b) (4). A BE study was conducted between vorapaxar tablets, 2.5 mg, containing high (b) (4) and low (b) (4) amounts of drug present as free base. Since vorapaxar exhibits pH dependent solubility, a proton pump inhibitor, pantoprazole, was co-administered to increase the ability to detect potential differences in bioavailability between tablets with low and high free base content owing to solubility differences of these tablets. Based on the results, the Applicant claims that similar exposure is achieved with tablets representative of the lower and upper base range of product administered to patients in the pivotal Phase 3 trials. A relative BA study was also conducted to evaluate the oral bioavailability of vorapaxar following administration of vorapaxar sulfate tablets with high free base levels (b) (4) relative to the reference tablets with free base levels of (b) (4). A PPI (pantoprazole) was included to assess the effect of reduced gastric acidity on the relative bioavailability of vorapaxar.

The formation of free base was studied at various stages of the manufacture and storage of vorpaxar tablets starting with the drug substance and formulation components:

- Vorapaxar sulfate drug substance converts to amorphous free base (b) (4)
-
-
-
-
-
-

- [REDACTED] (b) (4)

The drug product intended for marketing will be manufactured at Merck's Singapore site. [REDACTED] (b) (4) has been identified as a critical process parameter due to its known impact on free base in the product. In-process controls for the [REDACTED] (b) (4) have been established to control intermediate quality attributes that affect the final CQAs. The product specification includes the standard attributes for a solid oral dosage form i.e. appearance, identification, assay, degradation products, content uniformity and dissolution. Of note, there is a test for Free Base content with an acceptance criterion of [REDACTED] (b) (4). The test method is FT Raman. Batch analysis data have been provided for clinical and stability batches. Vorapaxar tablets will be packaged in blisters and bottles. The former is an aluminum blister with push-through aluminum lidding. The latter are white, opaque HDPE bottles with [REDACTED] (b) (4), foil [REDACTED] (b) (4) seal liner and desiccant.

The stability program consists of 2 studies of 3 batches each. Study #1 batches were manufactured at pilot scale prior to the implementation of the control strategy for free base formation during manufacture and storage whereas Study #2 batches were manufactured at commercial scale at the proposed commercial site with the intended controls in place. 24 months' of long term data are available for the former and 12 months for the latter. The same aluminum blisters were used in both studies, however, the bottles contained [REDACTED] (b) (4) desiccant in study #1 and [REDACTED] (b) (4) desiccant in Study #2. [REDACTED] (b) (4) and free base content were monitored in both studies. The Applicant claims that a 24 month shelf-life for storage at controlled room temperature is supported by the data provided.

Critical Review Issues

Drug Substance

- From the structure of vorapaxar, [REDACTED] (b) (4). Originally, this substance was called [REDACTED] (b) (4) but later in development the name was changed to vorapaxar sulfate. Has any rationale been provided for this?
- Regarding designation of Starting Materials
 - Is the justification provided for [REDACTED] (b) (4) as a starting material acceptable? It should be noted that although there [REDACTED] (b) (4) the free base of vorapaxar, all the chiral centers in the drug substance are established in [REDACTED] (b) (4). The Applicant was informed in the EOP2 CMC meeting that [REDACTED] (b) (4) may be acceptable as a starting material if 1) the synthesis of this material was provided and 2) any changes to the synthesis would be submitted for approval in a supplement (i.e. negotiated starting material). The applicant has fulfilled condition 1 but not 2. Is this acceptable?
 - Are the specifications for [REDACTED] (b) (4) adequate? Particular attention needs to be paid to the stereoisomer quality of this compound since it has 7 chiral centers and 128 possible stereoisomers. The scientific rationale for excluding many of the isomers from further study or inclusion in the specification should be evaluated.

- (b) (4) has also been designated a starting material and the justification for this should be reviewed. Although this is structurally much simpler than (b) (4) it is a final intermediate in the synthesis scheme so carry over of any impurities to the drug substance are more likely. Multiple routes of synthesis of (b) (4) are documented and it claimed that drug substance quality is independent of these variations. Is the specification of (b) (4) comprehensive, particularly with regard to impurities?
- Is the manufacturing process of the drug substance described in sufficient detail showing both critical and non-critical process parameters for the different steps? Are appropriate in-process controls in place?
- Regarding the specification:
 - Is the Applicant's exclusion of tests for (b) (4) acceptable?
 - From the specification one would not know this was a chiral substance since no enantiomeric purity or specific rotation test is proposed. Shouldn't the latter be included at least as an ID test?
 - Is the single point particle size acceptance criterion satisfactory considering the criticality of this attribute in free base formation during drug product manufacture?
 - Has the Applicant convincingly demonstrated that potential genotoxic impurities do not need to be monitored as part of the specification?
- Have the primary stability data been generated on production batches of the drug substance since the Applicant states that these fulfill the requirements for the post-approval commitment batches? It is noted that these primary batches are somewhat smaller in scale than the validation or more recent commercial batches.

Drug Product

- The main issue for the drug product is the late discovery of salt to free base conversion in vorapaxar tablets – For reference the reviewer should consult the CMC reviews in NDA 22307 for Effient (prasugrel) tablets where a similar conversion took place and led to extensive discussion within ONDQA and the Division of Cardiovascular and Renal Products as well as at the Center Director level.
 - Has the Applicant convincingly established that (b) (4), not excipients, is the main driver of the salt to free base conversion?
 - Given the poor choice of a (b) (4), what measures have been taken to minimize contact time with (b) (4). Has it been shown that the conversion can be minimized by adjusting process parameters for the (b) (4) (b) (4)?
 - Are the proposed limits of (b) (4) for free base content in the specification acceptable? Is there a logical reason for the lower limit (other than this was the range in Phase 3 batches within which bioequivalence was established)?
 - (b) (4) is a broad range for the acceptance criteria for conversion. Do recent batch data show wide variation in free base content within this range?
 - Is the analytical method for the determination of free base content adequately validated? What are the LOQ and LOD?

- Assuming this NDA is approved would a PMC be required to eliminate form conversion in keeping with NDA 22307?
- Who (Biopharm or Clin Pharm) will review the Biopharmaceutics studies related to form conversion?
- The dissolution method development report and the proposed specifications as well as the BCS Class 2 claim should be evaluated by the Biopharmaceutics reviewer.
- The Product Development section, including formulation development and manufacturing process development, should be evaluated in-depth to confirm that high quality product can be reproducibly manufactured at commercial scale.
- Is the manufacturing process described in adequate detail?
- Are the in-process controls for unit operations satisfactory?
- Should (b) (4) be listed in the specification with a footnote that this test is performed in-process?
- Regarding Stability:
 - Since amorphous free base can convert to the crystalline form which has even lower solubility, has the content of the crystalline free base been determined at various time points in either Stability Study 1 or 2? Is there convincing evidence that the crystalline form will not form in commercial scale batches even after storage for 24 months, the proposed shelf-life?
 - Have the patient in-use studies been performed with aged samples to show that product near the end of the shelf-life can be dispensed and used over a 90 day period without a significant increase in free base content?
 - Why are the bottle and blister long term storage conditions different in the stability studies and annual batch commitment?
 - Are the time points in the annual stability batch protocol sufficient?
 - Will the same tests be performed on the annual batches as those done on the primary batches?

Labeling

- The Applicant is not following the USP ‘salt policy’ that is currently in effect i.e. the established or non-proprietary name should be the active moiety vorapaxar and not the salt, vorapaxar sulfate. However, the strength, 2.5 mg, is for the salt and would translate into an inconvenient number for the active moiety (free base). How should this be resolved?
- USAN lists both salt and free base but the structure of vorapaxar is missing.

Comments and Recommendations

The application is fileable -- see attached Filing Check List. Facilities have been entered into EES; the reviewer should confirm the completeness of the entries. A categorical exclusion from environmental assessment has been requested. A Methods Validation request will be initiated shortly since this is an NME – Assay and Impurities by HPLC and Particle Size by Laser Diffraction for drug substance; Assay and Degradation Products by HPLC and Free Base Content by FT Raman for drug product. The reviewer has the option of requesting other methods, if warranted, later in the review cycle.

Kasturi Srinivasachar
Pharmaceutical Assessment Lead

June 13, 2013
Date

Ramesh Sood
Branch Chief

June 13, 2013
Date

PRODUCT QUALITY -- CMC and BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number: 204886 **NDA Type:** 1 **Established/Proper Name:** Vorapaxar Sulfate/Zontivity (proposed)
Original NDA, N-000

Applicant: Merck Sharp and Dohme **Letter Date:** May10, 2013 **PDUFA Goal:** May10, 2014
Stamp Date: May 10, 2013

CMC Reviewers: Thomas Wong

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		
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* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Some elements of QbD present
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		No master batch record
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any Comparability Protocols been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Some elements of QbD present
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		DMFs for packaging components

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		Fileable for Product Quality. See Biopharmaceutics Filing Review for fileability of the Biopharmaceutics Section
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
36.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			See Biopharmaceutics Filing Review
37.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		Salt nomenclature. Non-proprietary name to be changed to active moiety instead of salt.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KASTURI SRINIVASACHAR
06/13/2013

RAMESH K SOOD
06/14/2013

**ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW**

NDA Number	204,886
Submission Date	5/10/2013
Product name, generic of active(s)	Vorapaxar Sulphate
Dosage form and strengths	Tablets; 2.5 mg
Indication	Reduction of atherothrombotic events in patients with history of myocardial infarction, MI, but no history of stroke or transient ischemic attack, TIA.
Applicant	Merck
Clinical Division	DCRP
Type of Submission	505(b)(1) New Drug Application
Biopharmaceutics Reviewer	Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Team Leader	Sandra Suarez, Ph.D.
Acting Biopharmaceutics Supervisor	Richard Lostritto, Ph.D.

SUBMISSION

The drug is an NME and a first-in-class selective protease-activated receptor (PAR 1) antagonist. Vorapaxar was shown by the Applicant to block thrombin-mediated platelet aggregation, which is essential in reducing the risk of atherothrombotic complications of coronary disease.

The intended commercial dosage form is a 2.5 mg immediate-release tablet for once-daily dosing. The formulation is said to contain commonly used excipients that meet USP and Ph. Eur standards and does not contain novel excipients. The proposed manufacturing process is (b) (4)

(b) (4) he clinical trial formulation (CTM) is a white, round tablet while the proposed commercial (TBM) tablet is (b) (4) otherwise the same excipients, (b) (4) and manufacturing process are applicable to both products. The TBM tablet was bridged to the CTM tablet through in-vitro dissolution using the proposed method.

Vorapaxar is highly soluble in acidic pH below 4 but has low solubility in aqueous media between pH 4 – 7.5. In addition, the drug was demonstrated to have high permeability across Caco-2 cells. The Applicant therefore classifies Vorapaxar Sulphate as a BCS Class 2 compound. Vorapaxar Sulphate partially converts to the free base during the manufacturing process; the free base increases over long-term storage. The formation of vorapaxar base in the tablet is monitored by FT-Raman Spectroscopy at release and during stability. The Applicant has also performed two BA/BE studies on the drug product across a range of free base levels, demonstrating a decrease in bioavailability of the drug; the Applicant concludes that the decrease in bioavailability attributable to the base formation is unlikely to be clinically significant.

PROPOSED DISSOLUTION METHOD

**ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW**

Use of low actinic glassware or other means to protect from light.

Apparatus:	2 (paddles)
Dissolution Medium:	0.04M Na ₂ HPO ₄ , 1.5% w/v citric acid, pH 3.00 ± 0.05
Medium Volume:	900 mL
Medium Temperature:	37.0 ± 0.5°C
Rotation Speed:	50 rpm
Sampling Time:	60 minutes

(b) (4)

PROPOSED DISSOLUTION ACCEPTANCE CRITERION

Conforms to USP <711> or Ph. Eur. 2.9.3 with

(b) (4)

ONDQA - BIOPHARMACEUTICS INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
A. INITIAL OVERVIEW OF THE APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Is the dissolution test part of the DP specifications?	X		
2.	Does the application contain the dissolution method development report?		X	A brief method history is presented in section 3.2.P.5.6, subsection 6.0 but no details are provided on method development.
3.	Is there a validation package for the analytical method and dissolution methodology?	X		Section 3.2.P.5.3
4.	Does the application include a biowaiver request?		X	One strength, 2.5 mg, is proposed for commercialization.
5.	Is there information provided to support the biowaiver request?			N/A
6.	Is there information provided to assess dose dumping in the presence of alcohol?			N/A; formulation is immediate-release.
7.	Is discriminating power of the dissolution test demonstrated?		X	While elements of discriminating power seem to be scattered in formulation development report, no intentional experiments exist.
8.	Does the application include an IVIVC model?		X	N/A
9.	Is information such as BCS classification mentioned, and supportive data provided?		X	N/A
10.	Is information on mixing the product with foods or liquids included?		X	N/A
11.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		BA studies will be reviewed by OCP.
B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
12.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
13.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	-	-	The NDA is fileable from a Biopharmaceutics perspective.

**ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW**

ONDQA-BIOPHARMACEUTICS				
A. INITIAL OVERVIEW OF THE APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
14.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		Please see comments below. Also the clinical relevance of the solid stage change upon stability and the proposed specifications will be a review issue. This will be the purview of the CMC and biopharmaceutics review teams in consultation with the clinical review team.

FILING COMMENTS TO BE SENT TO THE APPLICANT

In order to facilitate the review of your NDA, please provide the following:

1. **Dissolution Test:** Submit the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

- a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. We recommend use of at least twelve samples per testing variable;
- b. Justify the choice of equipment, dissolution medium and rotation speed;
- c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);
- d. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., $\pm 10\text{-}20\%$ change to the specification-ranges of these variables). If available, provide data showing the capability of the proposed dissolution method and acceptance criterion to reject batches that are not bioequivalent.

2. **Dissolution Acceptance Criterion:** Provide the following data/information regarding the setting of dissolution acceptance criterion for your product:

- a. Tabulated individual vessel dissolution data for the pivotal clinical batches and primary (registration) stability batches used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value). Provide descriptive statistics at all sampling time points.

**ONDQA - BIOPHARMACEUTICS
INITIAL PRODUCT QUALITY ASSESSMENT AND FILING REVIEW**

b. You have predicted dissolution testing failure rates as justification of the proposed acceptance criterion. The use of accelerated stability data in predicting failure rates at the 45 and 60 minute time points is not acceptable. Please repeat the computations using room temperature stability data and submit the results to the NDA.

3. Bridging of the To-be-marketed (TBM) tablets to the Clinical Trial tablets (CTM):

Provide the individual vessel dissolution data, along with descriptive statistics, that bridge the proposed TBM product to the CTM. If the raw data permit, compute and report the f2 profile comparison.

{See appended electronic signature page}

Okpo Eradiri, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}

Sandra Suarez, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OKPONANABOFA ERADIRI
06/13/2013

SANDRA SUAREZ
06/14/2013