

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204886Orig1s000**

**OTHER REVIEW(S)**



## DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

### *Regulatory Project Manager Review*

**NDA:** 204886  
**Drug:** ZONTIVITY (vorapaxar) 2.08 mg Tablets  
**Class:** PAR-1 Antagonist  
**Applicant:** Merck, Sharpe, & Dohme  
**Proposed Indication:** **Patients with History of Myocardial Infarction (MI)**  
TRADEMARK is an antagonist of the protease-activated receptor-1 (PAR-1) indicated for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). TRADEMARK has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).

**FINAL Indication:** **Patients with History of Myocardial Infarction (MI) or with Peripheral Arterial Disease (PAD)**  
ZONTIVITY™ is indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).

**Date of Submission:** 10 May 2013  
**Approval date:** 8 May 2014  
**PDUFA date:** 10 May 2014

#### ❖ **REVIEW TEAM**

- Office of New Drugs, Office of Drug Evaluation I (ODE I)
  - Signatory Authority, ODE I
    - Ellis Unger, M.D. (Office Director)
  - Division of Cardiovascular & Renal Products (DCRP)
    - Norman Stockbridge, M.D., Ph.D. (Division Director)
    - Thomas Marciniak, M.D. (Cross-Discipline Team Leader - CDTL)
    - Martin Rose, M.D., JD (Clinical Reviewer - Efficacy)
    - Jon Levine, M.D. (Clinical Reviewer - Safety)
    - Patricia Harlow, Ph.D. (Non-clinical)
    - Alison Blaus, RAC (Regulatory Health Project Manager)
- Office of Clinical Pharmacology
  - Sudharshan Hariharan, Ph.D.
  - Bilal AbuAsal, Ph.D.
  - Fang Li, Ph.D.
- Office of Biostatistics, Division of Biometrics I
  - Yeh-Fong Chen, Ph.D.
- Office of New Drug Quality Assessment (ONDQA)
  - Thomas Wong, Ph.D. (Drug Substance / Drug Product)

- Okpo Eradiri, Ph.D. (Biopharmaceutics)
- Erika Pfeiler, Ph.D. (Microbiology)
- Office of Surveillance and Epidemiology
  - Kimberly Defronzo, RPh, MS, MBA (DMEPA)
  - Janine Stewart, PharmD (DMEPA)
  - Kimberly Lehrfield, PharmD (DRISK Team Leader)
  - Jamie Wilkins-Parker, PharmD (DRISK Reviewer)
- Office of Medical Policy
  - Office of Prescription Drug Promotion (OPDP)
    - Zarna Patel – Patient Labeling
  - Patient Labeling
    - Karen Dowdy, RN, BSN (Medication Guide)

#### ❖ **BACKGROUND**

ZONTIVITY (vorapaxar sulfate or SCH 53034), is an antagonist of the protease-activated receptor-1 (PAR-1) that inhibits thrombin-induced platelet aggregation. The applicant conducted two Phase 3 trials:

- **TRA•CER** - A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With Acute Coronary Syndrome. Patients in this trial were either randomized to placebo or 40mg loading dose of vorapaxar followed by a daily maintenance dose of 2.5mg.
- **TRA 2P/TIMI 50** - a multinational, multicenter, double blind trial to evaluate the efficacy and safety of vorapaxar in addition to standard of care, compared to placebo in addition to standard of care in the secondary prevention of ischemic events in patients with established atherosclerotic disease, as manifested by coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral arterial disease (PAD). The primary endpoint in this trial was the reduction in the incidence of cardiovascular death, myocardial infarction (MI), stroke and urgent coronary revascularization relative to standard of care alone. Patients in 2P were randomized to receive either 2.5 mg daily of vorapaxar or matching placebo.

TRA•CER was stopped for an increased risk of intracranial hemorrhage in subjects taking vorapaxar. Based on those results, subjects in TIMI 50 with a previous history of stroke/ICH were immediately discontinued from study drug.

We met with the applicant on two occasions to discuss this dossier. The first was a topline meeting to discuss the results from the Phase 3 trials (TRA•CER /TRA 2P) on 25 April 2012 (minutes dated 21 May 2012) and the second was a pre-NDA meeting on 19 June 2012 (minutes dated 2 July 2012).

#### ❖ **REGULATORY TIMELINE and GENERAL APPLICATION MILESTONES**

This section will cover a number of clinical development and general application milestones (pre- and post-NDA submission). The review of this application proceeded relatively smoothly, with approximately 91 information requests since 10 May 2013.

- IND received: 17 December 2004
- End of Phase 2 Meeting: 7 February 2007 (minutes dated 16 March 2007)
- There was no SPA of either TRA 2P or TRA•CER

- Top-Line Meeting: 25 April 2012 (minutes dated 21 May 2012)
- Pre-NDA Meeting: 19 June 2012 (minutes dated 2 July 2012)
- NDA Submission Received: 10 May 2013
- Filing Meeting: 10 June 2013
- 74-day Issues Letter with Comments: 22 July 2013
- Executive Carcinogenicity Assessment Committee (CAC) Meeting: 15 October 2013
- Mid-cycle Meeting: 24 October 2013
- Mid-Cycle Communication Meeting: 31 October 2013 (minutes dated 4 December 2013)
- Late-Cycle Briefing Book Finalized: 20 December 2013
- Late-Cycle Communication Meeting: 3 January 2014 (minutes dated 31 January 2014)
- Advisory Committee Meeting: 15 January 2014
- PDUFA Date: 10 May 2014
- **Approval Letter Date: 8 May 2014**

#### **User Fee**

The user fee for this application was paid in full on 10 April 2013, prior to the submission of the application (ID 3013228).

#### **Pediatric Review Committee (PeRC)**

The PeRC meeting to discuss this application was held on 20 November 2013. The applicant proposed a full waiver because the event rate of symptomatic atherosclerotic cardiovascular disease in the pediatric population is low. Further, given the number of patients and the duration of time needed to demonstrate a benefit on cardiovascular morbidity and mortality, it would not be of significant therapeutic benefit to conduct an outcome study with vorapaxar in the pediatric population. The PeRC and the Division agreed with this rationale. Therefore, a full pediatric waiver was granted for this application.

#### **Advisory Committee**

It was decided at the filing meeting and through internal discussions with various individuals within the Agency that an Advisory Committee (ADCOM) would be needed for this application [ZONTIVITY is a new molecular entity (NME) and the 1<sup>st</sup> drug in this class (PAR-1 antagonist)]. After being presented the data (from both the applicant and the Agency) and engaging in multiple discussion topics, when asked, “Should vorapaxar be approved?” the committee voted 10 (yes) to 1 (abstain). Please see the Agency’s quick minutes from this meeting for a summary of each discussion question.

#### **Trade name**

ZONTIVITY was deemed conditionally acceptable on 8 August 2013 and again on 31 January 2014.

#### **Review Status**

Due to the Phase 3 trial results from TRA 2P and TRA•CER, the applicant requested and was granted a standard review.

❖ **LABELING REVIEW**

Labeling discussions began in 5 February 2014 and were concluded on 8 May 2014. Please see the final label appended to the approval letter

**Risk Evaluation and Mitigation Strategy (REMS)**

With the initial application on 10 May 2013, the sponsor submitted a REMS (similar to the other agent in this area, prasugrel and ticagrelor). Upon review of the Phase 3 data, Dr. Wilkins-Parker concluded that risk mitigation measures beyond professional labeling were not warranted at this time. She continued to state that vorapaxar has proven to have a survival benefit for patients who have suffered an MI who have not had a stroke or TIA. Further, the prescriber population likely to prescribe vorapaxar is familiar with a relatively large class of currently marketed anti-platelet medications and their associated risk of bleeding; in particular, Effient (prasugrel), which also has an increased risk of ICH in susceptible patients, and had its communication plan REMS released. Please see her review dated 19 February 2014.

❖ **DISCIPLINE REVIEWS**

Below are the conclusions reached by the ZONTIVITY CDTL, Division Director and Office Director. Please refer to the individual discipline reviews for the primary reviewer's conclusions.

**Office Memorandum** (8 May 2014)

Dr. Unger finalized a memo on 8 May 2014 concurring with Dr. Stockbridge and the primary clinical reviews in recommending an approval for vorapaxar.

**Divisional Memorandum** (25 April 2014)

Dr Stockbridge drafted and finalized a review from the Division on 25 April 2014 concurring with the primary clinical reviewers recommending approval.

**Cross-Discipline Team Leader - CDTL** (18 April 2014)

Dr. Marciniak recommended approval of vorapaxar for the reduction of atherothrombotic events in patients with a history of MI or with PAD and without a history of stroke or TIA. He stated that he judged the favorable efficacy results of TRA 2P to be reliable enough and the increased bleeding to be tolerable such that the risk-benefit is favorable for the subgroups of history of MI and PAD. He further noted that the exclusion of patients with a history of stroke or TIA is justified by the increased ICH rates in TRA 2P for these patients as well as similar experiences with other platelet inhibitors such as prasugrel.

Dr. Marciniak recommended a post-marketing requirement (PMR) for a study on the effects of vorapaxar on bleeding time (alone and in various combinations with aspirin or clopidogrel). Upon internal discussion, The Division decided not to require a study because information on bleeding time would not add useful data beyond what is already known about the pharmacodynamic effects of the drug.

❖ **CONSULT REVIEWS**

Please see the following consults that were requested during the NDA review and the corresponding date they were finalized:

- Division of Ophthalmology: 29 October 2013 and 5 May 2014
- OSI (Clinical Audit): 20 March 2014
- OSI (Bioequivalence Audit): 29 April 2014
- DMEPA (Tradename): 9 August 2013 and 24 January 2014

- DMEPA (Carton-Container Labeling): 14 February and 28 March 2014
- DRISK (REMS): 19 February 2014
- Patient Labeling (Medication Guide): 2 May 2014
- Office of Prescription Drug Promotion (OPDP): 1 May 2014

❖ **CONCLUSION**

After taking into consideration all of the primary reviews, consults, and the applicant's additional analyses, the Agency issued an approval letter for NDA 204886 on 8 May 2014. The approval letter was drafted for Dr. Ellis Unger's signature, but due to technical difficulties, Dr. Robert Temple signed the letter.

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/s/  
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ALISON L BLAUS  
05/12/2014

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

**PATIENT LABELING REVIEW**

Date: May 2, 2014

To: Norman Stockbridge, MD, PhD  
Director  
**Division of Cardiovascular and Renal Products (DCRP)**

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

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

From: Karen Dowdy, RN, BSN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Zarna Patel, Pharm.D.  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ZONTIVITY (vorapaxar)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: NDA 204-886

Applicant: Merck Sharp & Dohme Corp.

## 1 INTRODUCTION

On May 10, 2013, Merck Sharp & Dohme Corp. submitted for the Agency's review original New Drug Application (NDA) 204-886 for ZONTIVITY (vorapaxar) Tablets, with the proposed indication for the reduction of atherothrombotic events in patients with a history of myocardial infarction.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Cardiovascular and Renal Products (DCRP) on May 16, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ZONTIVITY (vorapaxar) Tablets.

## 2 MATERIAL REVIEWED

- Draft ZONTIVITY (vorapaxar) Tablets MG received on February 5, 2014, and received by DMPP and OPDP on April 24, 2014.
- Draft ZONTIVITY (vorapaxar) Tablets Prescribing Information (PI) received on May 10, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 24, 2014.
- Approved BRILINTA (ticagrelor) comparator labeling dated December 13, 2013.
- Approved Effient (prasugrel) comparator labeling dated November 18, 2013.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

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

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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/s/  
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KAREN M DOWDY  
05/02/2014

ZARNA PATEL  
05/02/2014

BARBARA A FULLER  
05/02/2014

LASHAWN M GRIFFITHS  
05/02/2014

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

Memorandum

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**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** May 1, 2014

**To:** Alison Blaus  
Regulatory Project Manager  
Division of Cardiovascular and Renal Products

**From:** Zarna Patel, Pharm.D.  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **Zontivity (vorapaxar) Tablets**  
NDA: 204886  
Comments on draft product labeling

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OPDP has reviewed the proposed Package Insert (PI) submitted for consult on May 16, 2013, for Zontivity (vorapaxar) Tablets (Zontivity). As requested, OPDP's comments are provided directly on the attached "clean" copy of the proposed labeling emailed to us on April 23, 2014.

OPDP has also reviewed the revised Carton and Container Labeling submitted by the sponsor on March 14, 2014. We have no additional comments on the revised Carton and Container Labeling at this time.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Zarna Patel at 301.796.3822 or [zarna.patel@fda.hhs.gov](mailto:zarna.patel@fda.hhs.gov).

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ZARNA PATEL  
05/01/2014

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: April 29, 2014

TO: Norman Stockbridge, M.D.  
Director  
Division of Cardiovascular and Renal Products (DCRP)  
Office of Drug Evaluation 1  
Office of New Drugs

FROM: Gopa Biswas, Ph.D., Pharmacologist  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations (OSI)

and

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIRs covering NDA 204-886, Vorapaxar sulfate  
(SCH 530348) 2.5 mg tablets, sponsored by Merck & Co.

At the request of the Division of Cardiovascular and Renal Products (DCRP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an inspection of the clinical and analytical portions of the following bioequivalence study:

**Study Number:** P06558  
**Study Title:** "A study to determine the bioequivalence of SCH 530348 2.5 mg tablets containing a high and low percentage of drug as the free base within the range used in the pivotal phase 3 efficacy and safety trials"

The bioanalytical portion of the study was conducted by Schering-Plough Research Institute, which merged with Merck Research Laboratories (MRL) in November 2009. The audit included a thorough review of study records, and interviews and discussions with the firm's current management and staff.

The inspection of the clinical portion Brading (ORA Investigator, DAL-DO) at [REDACTED] (b) (4) April 8-15, 2014. There were no objectionable findings during the inspection and Form FDA-483 was not issued. The inspection of the analytical portion was conducted by Gopa Biswas (DBGLPC Scientist) and Peter Lenahan (ORA Investigator, NWJ-DO) from August 12-16, 2013 at MRL. Form FDA-483 containing inspectional observations was issued at the conclusion of the inspection (**Attachment 1**). The response from Merck to the inspectional observations was received on August 29, 2013 (**Attachment 2**).

The Form FDA-483 observations, Merck's response to Form FDA-483 and my evaluations follow:

- 1a) Failure to use quality control (QC) sample concentrations that were representative of SCH 530348 concentrations in plasma samples of study subjects. Specifically, the maximum observed concentrations of SCH 530348 in the study ranged from 11.5 ng/mL to 49.3 ng/mL but the QC concentrations used were 3.0 ng/mL, 80.0 ng/mL and 800.0 ng/mL.**

**Merck's Response:**

The response acknowledged the observation but claimed that their data at 3 and 80 ng/mL are accurate and the method is sufficiently sensitive to support the bioequivalence study. The firm presented a table of estimated plasma concentrations to show the percentage of samples within the concentration range 1 to 50 ng/mL (Table 1 in **Attachment 2**).

**DBGLPC Assessment:**

The measurable concentrations of vorapaxar in plasma samples were between 1 and 50 ng/mL during the study P06558. The 800 ng/mL QC sample is not representative of the drug concentrations in study samples; therefore, it does not contribute to the accurate determination of subject samples during the study. The FDA Guidance on Bioanalytical Method Validation recommends three different QC concentrations in the range of study sample concentrations. The firm failed to incorporate an additional QC concentration upon seeing early

concentration results. However, the 3 and 80 ng/mL QC samples performed well during the study.

In my opinion observation 1a does not have significant impact on the accuracy of measured vorapaxar concentrations in study plasma samples.

- 1b) Failure to use calibration standards and quality control (QC) sample concentrations that were representative of SCH 2046273 concentrations in plasma samples of study subjects. Specifically, the maximum observed concentrations of SCH 2046273 in this study ranged from 0.502 to 2.18 ng/mL, but QC samples were 1.5, 40, and 400 ng/mL. Calibration standards were 0.5, 1, 2, 5, 10, 25, 50, 200, 425, and 500 ng/mL.**

**Merck's Response:**

The response acknowledged observation 1b and stated that the determination of the metabolite SCH 2046273 concentration was for exploratory purposes only. Nevertheless, the firm claims that the data are accurate because few (b) (4) of the QC results failed acceptance criteria at (b) (4) within a factor of three of all measurable concentrations.

**DBGLPC Assessment:**

The measurable concentrations of metabolite SCH 2046273 were in the four-fold range spanning only three calibrators and one QC sample. There would not have been any benefit from additional calibrator and QC concentrations of SCH 2046273 in this narrow range. A significant number of sample concentrations were below the limit of quantitation (<0.5 ng/mL).

In my opinion the accuracy of most SCH 2046273 concentrations in study plasma samples is not assured, because the observed concentrations were below the limit of quantitation.

**Conclusion:**

Following review of the inspectional findings and Merck's response, I recommend that:

- The results from the clinical portion and vorapaxar (SCH 530348) concentrations from the analytical portion of study P06558 are acceptable for Agency review.
- The bioanalytical method for SCH 2046273 was insufficiently sensitive to precisely describe the pharmacokinetic profile

of this metabolite following dosing with vorapaxar,  
SCH 530348.

Gopa Biswas, Ph.D.  
Bioequivalence Branch, DBGLPC, OSI

**Final Classifications:**

(b) (4)

**Merck Research Laboratory, Summit, NJ- VAI  
(FEI# 3008510631)**

**CC:**

CDER OSI PM TRACK  
OSI/DBGLPC/Taylor/Dejernett/CF  
OSI/DBGLPC/BeB/Haidar/Choi/Skelly/Biswas  
CDER/OND/ODEI/DCRP/Alison Blaus/Sudarshan Hariharan/Stockbridge  
ORA/NWJ-DO/Lenahan  
Draft: GB 10/1/2013  
Edit: AD 10/9/2013; YMC 10/9/2013; MFS 10/9/2013; 4/28/14; WHT  
4/29/2014; SHH 4/29/2014  
OSI: BE File # 6470; O:\BE\EIRCOVER\204886mer.vor.doc  
ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
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GOPA BISWAS  
04/29/2014

SAM H HAIDAR  
04/29/2014

WILLIAM H TAYLOR  
04/29/2014

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**LABEL AND LABELING MEMO**

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

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

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**Date :** March 28, 2014  
**Requesting Office or Division:** Division of Cardiovascular & Renal Products (DCRP)  
**Application Type and Number:** NDA 204886  
**Product Name and Strength:** Zontivity (vorapaxar) tablets, 2.08 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Merck Sharp & Dohme Corp.  
**Submission Date:** March 14, 2014  
**OSE RCM #:** 2013-1568-1  
**DMEPA Primary Reviewer:** Janine Stewart, PharmD  
**DMEPA Team Leader:** Lisa Khosla, PharmD, MHA

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## **1 INTRODUCTION**

This memorandum evaluates the revised labels and labeling for Zontivity (vorapaxar), NDA 204886, submitted on March 14, 2014 (Appendix A). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-1568 dated February 14, 2014.

## **2 MATERIAL REVIEWED**

DMEPA reviewed labels and labeling submitted on March 14, 2014. We compared the revised labels against the recommendations contained in OSE Review # 2013-1568 dated February 14, 2014.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

The revised labels adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Karen Bengtson, at 301-796-3338.

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JANINE A STEWART  
03/28/2014

LISA V KHOSLA  
03/28/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL INSPECTION SUMMARY

**DATE:** March 14, 2014

**TO:** Martin Rose, Medical Officer  
Alison Blaus, Regulatory Health Project Manager  
Division of Cardio-Renal Drug Products

**FROM:** Sharon K. Gershon, Pharm. D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Susan Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 204886

**APPLICANT:** Merck Sharp & Dohme Corp.

**DRUG:** Zontivity™ (vorapaxar sulfate)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Priority

**INDICATION:** the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI)

**Protocol:** No. P04737: A Multicenter, Randomized, Double-blind, Placebo-controlled, Study to Evaluate the Safety and Efficacy of Vorapaxar (SCH530348) in Addition to Standard of Care in Subjects With a History of Atherosclerotic Disease: Thombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P – TIMI 50)

CONSULTATION REQUEST DATE: July 29, 2013

INSPECTION SUMMRY GOAL DATE: March 20, 2014

ADVISORY COMMITTEE January 15, 2014

DIVISION ACTION GOAL DATE: May 10, 2014

PDUFA DATE: May 10, 2014

## **I. BACKGROUND:**

Merck Sharp & Dohme Corp (subsidiary of Merck & Company, Inc.) submitted NDA 204886 for vorapaxar sulfate tablets (2.5 mg) requesting an indication to reduce atherothrombotic events in patients with a history of myocardial infarction (MI).

Atherosclerosis and ischemic cardiovascular (CV) diseases like coronary artery disease (CAD) are progressive systemic disorders in which clinical events are precipitated by episodes of vascular thrombosis. Patients with an established history of atherothrombotic or athero-ischemic disease are at particular risk of future cardiac or cerebral events, and vascular death.

Vorapaxar is a first-in-class selective antagonist of the protease-activated receptor-1 (PAR-1). PAR-1 is the primary thrombin receptor on human platelets, mediating the downstream effects of thrombin on platelets. Thrombin is a critical coagulation factor in hemostasis and thrombosis. Thrombin-induced platelet activation has been implicated in a variety of cardiovascular disorders including thrombosis, atherosclerosis, and restenosis following percutaneous coronary intervention. As an antagonist of PAR-1, vorapaxar blocks thrombin-mediated platelet aggregation and thereby has the potential of reducing the risk of atherothrombotic complications of coronary disease.

The sponsor submitted data from an international, multicenter, randomized, double-blind, placebo-controlled trial that was conducted at 1032 study sites in 32 countries, and enrolled 26,449 subjects. The trial was TRA 2°P - TIMI 50 trial (Protocol P04737) which used the oral administration of oral vorapaxar in the secondary prevention of ischemic events in subjects with atherosclerosis involving the coronary, cerebral, or peripheral vascular systems. In this trial, the sponsor claimed that Vorapaxar reduced the rate of a combined endpoint of cardiovascular death, myocardial infarction, stroke, and urgent coronary revascularization.

Following randomized treatment assignment, subjects were to return after 30 days, 4, 8, and 12 months, and every 6 months thereafter for scheduled evaluations until the end of the study; that is, when a pre-specified defined number of subjects had efficacy endpoint events and every subject had the opportunity to participate in the study for at least 1 year.

The primary efficacy endpoint of the study was the time from randomized treatment assignment to the first occurrence of any component of the composite of cardiovascular death, MI, stroke, and urgent coronary revascularization.

The key secondary endpoint of the study was the time from randomized treatment assignment to the first occurrence of any component of the composite of cardiovascular death, MI, and stroke. Secondary safety endpoints were based on measures of bleeding, including composite of moderate and severe bleeding events according to GUSTO classification, and clinically significant bleeding, defined as TIMI major or TIMI minor bleeding, or bleeding that requires unplanned medical treatment, surgical treatment, or laboratory evaluation.

**Reasons for Site Selection:** In our discussions with the review division, we chose sites with relatively high enrollment. In addition:

- Site #1010 (Burgess) had an exceedingly low rate of bleeding events and a high rate of discontinuation of follow-up
- Site #2513 (Friedrich) had an exceedingly low rate of bleeding events
- Site #3456 (Syam) had a notable excess of primary endpoint events in the placebo arm
- Site #1722 (Bar) had an exceptionally low rate of treatment completion
- Site #3583 (Korban) had high enrollment and a notable excess of primary endpoint events in the placebo arm.

## II Results

Name of CI/Address	Protocol # and # of Subjects	Inspection Dates	Final Classification
Lesley Burgess, MB.Ch.B. & Jennifer Vergotine TREAD Research cc Francie van Zijl Drive Room 41, 8th Floor Tygerberg Hospital Department of Cardiology Parow 7500 South Africa	Protocol #P04737  Site #1010  264 subjects	November 18 – 22, 2013	NAI
Mauricio Andre Gheller Friedrich Hospital Sao Lucas da PUCRS Avenida Ipiranga, 6690 sala 220 Departamento de Neurologia Porto Alegre 90610-000 Brazil	Protocol #P04737  Site #2513  200 subjects	December 9 – 13, 2013	Pending  (Preliminary VAI)
Gurcharan Syam Gurcharan S Syam Medicine	Protocol #P04737	February 24 - 28, 2014	Pending

Professional Corporation 430 Notre Dame Ave Sudbury, Ontario P3C 5K7 Canada	Site #3456  158 subjects		(Preliminary VAI)
Michael Bar NSZ BORMED Neurologicka ambulance Trebovicka 5114 Ostrava-Trebovice 722 00 Czech Republic	Protocol #P04737  Site #1722  173 subjects	December 16- 20, 2013	Pending  (Preliminary VAI)
Elie Korban Kore Cardiovascular Research 9486 HWY 412 West Lexington, TN 38351 Other locations: Heart and Vascular Center West TN Savannah 985A Wayne Road Savannah, TN 38372	Protocol #P04737  Site #3583  107 subjects	December 18 – 29, 2013	NAI
Merck, Sharpe & Dohme Corp. 321 Norristown Rd., Suite 320 Ambler, PA	Sponsor Inspection	December 9 – 20, 2013	VAI

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

#### **1. Lesley Burgess (Site #1010)**

TREAD Research cc Francie van Zijl Drive Room 41  
Department of Cardiology  
Parow 7500 South Africa

**a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Lesley Burgess has 15 IND in the CDER database and no prior inspections. The site screened and enrolled 264 subjects. A total of 222 subjects completed the study; five subjects withdrew consent and 37 subjects died. The first subject signed the Informed Consent Document (ICD) on July 28, 2008. The last subject was contacted in September 2011.

The site discontinued the study drug in subjects with a prior history of stroke or a stroke that occurred during the study, as instructed by the sponsor in a memo dated January 13, 2011. The memo followed the DSMB review of the study and their recommendation, following an

interim analysis in January 2011, to discontinuing study drug in all subjects with a prior history of stroke, or a stroke occurring during the course of the study. At this site, five subjects had a stroke during the study and 22 subjects had a history of stroke, and thus were removed from study drug. These 27 subjects were contacted and followed with final visit procedures, according to instructions.

The FDA field investigator reviewed records for 66 subjects during the inspection. The record review included corroboration of adverse events, primary efficacy endpoint data, and protocol deviations with the data listings. Other study records audited included (but were not limited to): ethic review committee approvals; monitoring reports; site signature and responsibility logs; and site training logs. The FDA field investigator reviewed the electronic Case Report Forms (eCRFs) for ten subjects, and corroborated them with the data listings provided with the assignment.

**b. General observations/commentary:** The FDA field investigator observed that the site reported all adverse events electronically as they became aware of them, and also kept a log of all adverse events in the subject's study file. She noted that whereas some adverse events were not listed in the data listings, the site's rationale was that the sponsor consolidated some of the AEs into a specific condition or disease state. She was able to verify and corroborate the primary efficacy endpoints in the data listings with the source documents. Drug accountability records were audited including a review of receipt records, inventory records, study drug use, and final accountability records. No discrepancies were noted. No Form FDA 483 was issued at the conclusion of the inspection.

**c. Assessment of data integrity:** In general, very minor recordkeeping discrepancies were found during this inspection, and they were discussed with staff at the conclusion of the inspection. The study was conducted well at this site, and OSI recommends that the data are acceptable in support of the claimed indication

**Note:** Observations noted below for the following three foreign clinical investigator sites are based on the Form FDA 483 and communications with the field investigator. An addendum to this inspection summary will be generated if conclusions change upon receipt and review of the establishment inspection report (EIR).

## **2. Mauricio Andre Gheller Friedrich (Site #2513)**

Hospital Sao Lucas da PUCRS  
Avenida Ipiranga, 6690 sala 220  
Departamento de Neurologia  
Porto Alegre 90610-000 Brazil

**a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Friedrich has one IND in the CDER database and no prior inspections. The site screened 206 subjects, of which 200 subjects were randomized. A total of 183 subjects completed the study at this site. The first subject was screened on August 25, 2008 and randomized on August 26, 2008. The last subject was contacted by telephone on November 24, 2011.

The FDA field investigator reviewed the following study records: ethic review committee approvals; monitoring reports; site signature and responsibility logs; site training logs; drug accountability records that included receipt records, inventory records, study drug use, and final accountability records; the initial and updated ICDs) for 12 subjects; inclusion and exclusion criteria eight subjects; and all adverse and serious adverse events for twelve subjects. She also reviewed prior study medication records for eight subjects and concomitant medications taken during the study for twelve subjects. Finally, she reviewed and corroborated source records and data listings for all discontinued subjects, subject withdrawals, protocol deviations, and primary and secondary efficacy endpoint events.

**b. General observations/commentary:** Source documentation was paper based. The site maintained documentation of subject communications and had various worksheets to record information during subject visits. The field investigator reported that subject source documents were organized, legible and complete. Electronic records were not used as source documentation. The site entered data into the sponsor database in a timely manner.

All eight subjects audited met the inclusion and exclusion criteria. However, the subjects screening ECGs and lab results were not signed as reviewed until after randomization. For example:

- Subject 004298 was screened and randomized on October 30, 2008. The screening ECG and laboratory results for Subject 004298 were not signed as reviewed until November 3, 2008.
- Subject 33902 was screened and randomized on July 29, 2009. The screening ECG and laboratory results for Subject 33902 were not signed as reviewed until August 3, 2009.

No discrepancies were noted in the review of adverse and serious adverse event information for twelve subjects. Adverse event information was properly reported.

The field investigator reported that adequate documentation existed to ensure that all subjects were alive and available for the duration of their study participation. Subject records contained acceptable observations. The records documented the subject's exposure to the test article. She observed that observations were made throughout the study conduct including lab test results and unrelated illnesses by the clinical investigator and the sub-investigators.

The FDA field investigator noted that the sponsor's data table indicated 14 subjects (3 in the placebo group and 11 in the study drug group) withdrew from the study, whereas the site indicated that only 2 subjects (Subject 004298 and Subject 033902, and both receiving study drug), withdrew from the study. According to the sponsor this discrepancy was because the IVRS system did not differentiate between subjects that withdrew from treatment and did not agree to further follow-up and subjects that withdrew from treatment but did agree to future follow-up contact.

The field investigator found the following regulatory violations:

**An investigation was not conducted in accordance with the investigational plan.**

Specifically,

1. For 12 of 12 subject records reviewed, the site failed to use the appropriate ethics committee approved version of the ICD for the initial consent, or for re-consenting subjects. For example:
  - Subjects 13354, 08070 and 08076 initially signed the ICD in May 2009 and signed ICD Version 3 dated July 21, 2008. The ICD Version 4.0 dated January 9, 2009 was the ethics committee approved version at the time, and should have been signed at screening.
  - Subjects 31094, 51404, and 30857 did not sign the ICD Version 4.0 dated January 9, 2009 at their next scheduled visit. The subjects did not sign the revised ICF until March 2010.

In his January 7, 2014 response letter, Dr. Friedrich acknowledged this observation, and indicated that his site had implemented corrective action - use of an ICD tracking tool to ensure that the most recent ICD is used for the initial and re-consenting of subjects.

2. The site failed to ensure that a revised version of the ICD which contained important new safety information was reviewed and approved by the Ethics Committee in a timely manner. The new ICD version 2.1 dated April 5, 2011 was approved on August 4, 2011.

In his January 7, 2014 response letter Dr. Friedrich acknowledged this observation and promised a plan for corrective action.

3. The site failed to report all concomitant medications taken during the hospitalization of Subject 31094. During the subject's hospitalization between May 17 and 28, 2010 the medical chart documented the administration of heparin IV, furosemide IV, and hydrocortisone IV. These medications were not reported to the sponsor as concomitant medications.

In his January 7, 2014 response letter Dr. Friedrich acknowledged this observation and promised a plan for corrective action.

**c. Assessment of data integrity:** Although a few regulatory violations were observed during the inspection, they are unlikely to significantly impact data integrity. In general, the study was conducted well at this site, and OSI recommends the data as acceptable in support of the claimed indication.

### **3. Gurcharan Syan (Site 3456)**

Gurcharan S Syan Medicine  
Professional Corporation  
430 Notre Dame Ave  
Sudbury, Ontario Canada

**a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Syan has eight IND studies in the CDER database and no prior inspections. The site screened 158 subjects all of which all were randomized. A total of 88 subjects completed the study at this site.

The FDA field investigator thoroughly reviewed records for 29 subjects: twenty subjects were selected from the protocol deviations listed and determined to be significant, and the remaining nine records were the last nine subjects enrolled to determine if corrective action had been implemented.

**b. General observations/commentary:** The FDA field investigator reported that all Serious Adverse Events (AEs) were reported, but that the site seemed to neglect reporting some AEs in the progress notes or some AEs documented in physical examinations. She also observed that because the site did not obtain a detailed subject medical history it was sometimes difficult to determine if events documented in the source records were new events or an event that occurred prior to subject study entry, such as headaches or cataracts. This item was listed on the Form FDA 483.

The FDA field investigator reported the endpoint efficacy data was verifiable, and that all endpoint events appeared to be accurately reported. Protocol deviations were verified. The majority of the deviations occurred during the first year of the study. The site improved over time in regards to better documentation practices. She observed that some deviations reported in the data listings were not true deviations. The site did well in regards to complying with required visits and required procedures. For subject records reviewed, there were no missing ECGs, no missing vital signs, and no missing physical examinations. She observed all subjects as very compliant with visit schedules, despite traveling from Northern Ontario.

At the conclusion of the inspection an FDA 483 was issued for **failure to follow the investigational plan**. The inspection found the following deficiencies:

1. The site failed to report Serious Adverse Events (SAEs) within one day. For example:
  - Subject 3319 was hospitalized for pneumonia [REDACTED] (b) (6)  
The site became aware of the SAE on September 3, 2009, but did not enter the SAE into the e-CRF until September 21, 2009, almost three weeks later.
  - Subject 12349 was hospitalized for Crohn's disease [REDACTED] (b) (6)  
The site became aware of the SAE on July 12, 2010, but did not enter this into the e-CRF until July 22, 2010, ten days later.
  - Subject 51386 was hospitalized for nausea, diarrhea and pneumonia [REDACTED] (b) (6)  
[REDACTED] The site became aware of the SAE on November 23, 2009, but did not enter into the eCRF until June 22, 2010, seven months later.

2. The inclusion criteria required that subjects have evidence or a history of atherosclerosis involving the coronary, cerebral or peripheral vascular systems. The following subjects did not meet this inclusion criterion, and were randomized to treatments:
  - Subject 51384 was randomized and dispensed study drug on October 6, 2008 although the subject had an ankle brachial index (ABI) of 0.89 (protocol required ABI < 0.85)
  - Subject 12349 was randomized and dispensed study drug on January 28, 2009 although there was no documentation of hospitalization with diagnosis of myocardial infarction.
3. The exclusion criteria excluded subjects with concurrent or anticipated treatment with warfarin. Subject 050712 was randomized on June 11, 2008 even though documents showed that the subject had been taking Coumadin since 1998.
4. The protocol required reporting adverse events which may include the onset of new illness or the exacerbation of pre-existing conditions. Several adverse events were not reported. For example:
  - Subject 006440 reported ED during the End of Treatment visit on August 4, 2011.
  - Subject 010250 had neck bruit during the End of Treatment visit physical examination on September 13, 2011.

**c. Assessment of data integrity:** Although several instances were observed where the clinical investigator failed to follow the investigational plan, they are unlikely to significantly impact the primary efficacy or safety outcome of this study. The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

#### **4. Michael Bar (Site #1722)**

Neurologicka ambulance  
Trebovicka 5114  
Ostrava-Trebovice, Czech Republic

**a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Michael Bar has two IND studies in the CDER database and no prior inspections. The site screened 173 subjects all of which all were randomized. A total of 171 subjects completed the study at this site. The first subject was screened on September 30, 2008. The last subject had study contact via telephone follow-up on August 10, 2011.

The FDA field investigator reviewed the following study records: Ethic Review Committee approvals; monitoring logs and monitoring follow-up letters; site signature and responsibility

logs; and site training logs. Drug accountability records were audited including a review of receipt records, inventory records, study drug use, and final accountability records. The initial informed consent documents (ICD) were reviewed for 20 subjects, and the repeat ICD of subjects during the trial was reviewed for seven subjects. Inclusion and exclusion criteria were reviewed for eight subjects. Adverse events and serious adverse event (SAE) information was reviewed for eight subjects. Prior study medical records and concomitant medications were reviewed for eight subjects. The sponsor's data tablets were verified for discontinued subjects, primary efficacy endpoints, secondary efficacy endpoints, protocol deviations and subject withdrawals for eight subjects.

**b. General observations/commentary:** The sponsor data tables for Discontinued Subjects, Protocol Deviations, Primary Endpoints, Secondary Endpoints, and Withdrawals were audited. No deviations were noted in these records.

No subjects were found that did not meet the inclusion and exclusion criteria. The site was adequately monitored throughout the study. Many monitoring visits occurred between October 6, 2008 and February 7, 2012.

The FDA field investigator reported that subject source documents were organized, legible and complete. Source documentation was paper based. The site maintained documentation of subject communications and had various worksheets to record information during subject visits. The site entered data into the sponsor database in a timely manner. Financial reports were submitted to the sponsor prior to study enrollment at this site. For subject records reviewed, adverse event information was properly reported. Adequate documentation existed to ensure that all subjects were alive and available for the duration of their study participation. Subject records contained acceptable observations throughout study participation, including lab test results, test article administration, and unrelated illnesses by the clinical investigator. .

At the conclusion of the inspection an FDA 483 was issued for **failure to follow the investigational plan**. The inspection found the following deficiencies that were included in the FDA-483:

1. The site failed to properly obtain updated ICDs from two of the eight subjects reviewed at their next study visit. For example, Subjects 31049 and 31205 were seen at their eight-month visit in June 2009, but did not sign the ICD Version 3.0 until their 12-month visit of October 2009.
2. The site failed to correctly report all previous and concomitant medications for four of the eight subjects reviewed.

For example:

- Subject 31767: source documents included concomitant medications amiodarone and fluvastatin, which were not included in the e-CRF; and
- Subject 32136: source records documented concomitant medications such as enoxaparin and simvastatin, which were not included in the e-CRF.

3. The site failed to notify the sponsor of an SAE within 24 hours for three subjects. Specifically,
- For Subject 31767, during the 12-month visit on December 16, 2009 the site became aware that on [REDACTED] (b) (6) the subject was hospitalized due to atrial fibrillation. The site did not report this to the sponsor until December 21, 2009.
  - For Subject 32136, during the 8-month visit on October 21, 2009 the site became aware that the subject was hospitalized in [REDACTED] (b) (6) for heart failure. The site did not report this to the sponsor until January 21, 2010.
  - For Subject 32288, during the 8 month visit on October 8, 2009 the site became aware that the subject was hospitalized in [REDACTED] (b) (6) due to sick-sinus syndrome (tachycardia-bradycardia form). The site did not report this to the sponsor until October 15, 2009.

*Reviewer Comments: In his response letter, Dr. Bar indicated that the error in reporting SAEs was caused by one sub-investigator who was responsible for these three subjects. This response is not acceptable, because in signing the Form 1572, Dr. Bar was committing to being ultimately responsible for ensuring that all SAEs were reported in a timely manner to the sponsor.*

**c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

#### **5. Elie Korban (Site 3583)**

Kore Cardiovascular Research  
9486 HWY 412 West Lexington, TN 38351  
Other location: Heart and Vascular Center West TN Savannah  
985A Wayne Road  
Savannah, TN 38372

**a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. Dr. Elie Korban has eight INDs in CDER's COMIS database and no prior inspections.

The site screened 107 subjects, and there were no screen failures. A total of 86 subjects completed the study. The reasons for subjects who did not complete the study were as follows: four subjects withdrew consent, two subjects were withdrawn because of stroke, four subjects died during the study, ten subjects withdrew but were continued with telephone follow-up, and one subject was lost to follow-up.

Because of the large number of study subjects, the FDA field investigator reviewed records for 27 subjects (25% of the total number screened) for verification of the primary and secondary

efficacy endpoints, and for all adverse events, including all clinically significant moderate and severe bleeding events. She reviewed the informed consent documents for all subjects. She reviewed signed copies of the Form 1572's, and financial disclosure forms. She verified that all subjects met the inclusion and exclusion criteria. She reviewed receipt, dispensing and return of the study drug. She verified that source documents were consistent with the Case Report Forms (CRFs) for the primary efficacy endpoints, adverse events and serious adverse events, subject randomizations, protocol deviations, discontinuations, and concomitant medications.

**b. General observations/commentary:** In her review of the ICD, financial disclosure statements, and Form 1572's, she found no issues or deficiencies. For records reviewed, all subjects met the inclusion and exclusion criteria. There were no discrepancies in documentation of study drug accountability and disposition. She found that source documents corroborated with the case report forms and data listings for the primary efficacy endpoints, adverse events and serious adverse events, protocol deviations, discontinuations and concomitant medications. She noted several protocol deviations for out-of-window visits. She reported that all protocol deviations were well addressed and documented in the subject records. She also noted reasons for early terminations of subjects were well documented. No Form FDA 483 was issued at the conclusion of the inspection.

**c. Assessment of data integrity:** The study was conducted well at this site, and OSI recommends that the data is acceptable in support of the claimed indication.

## **6. Merck Sharp & Dohme Corp.**

126 E. Lincoln Avenue, Mailstop RY33-204  
P.O. Box 2000  
Rahway, NJ 07065-0900  
ClinForce

**a. What was inspected:** The current inspection was conducted between December 9 and December 20, 2013, and focused on the following five clinical investigator sites:

- Site #3583, Dr. Elie Korban (TN, 107 subjects)
- Site #1010, Dr. Lesley Burgess (So. Africa, 264 subjects)
- Site #2513, Dr. Mauricio Andre Gheller Friedrich (Brazil, 200 subjects)
- Site #3456, Dr. Gurcharan Syan (Canada, 158 subjects)
- Site #1722, Dr. Michael Bar (Czech Republic, 173 subjects)

During the inspection the FDA field investigators reviewed the following areas with regard to study Protocol TRA 2°P – TIMI 50: firm's training program for clinical investigators, study coordinators and monitors; financial disclosure statements; IRB/Ethic Committee approvals for the five clinical investigator sites covered during the inspection; Schering-Plough Transfer of Obligation to CROs and other organization service agreements; electronic CRFs and site files for the five clinical investigator sites covered during the inspection; Data Safety Monitoring Board (DSMB) Charter and meeting minutes; TIMI Study Group Memorandums; Clinical Endpoint Committee (CEC) Manual of Operations and meeting minutes; letters of termination

for five investigator sites terminated during the study (Drs. Makam, Griffin, Robson, Castano, Berthezene); Adverse Event Reports for selected sites; Annuals Reports; Certificate of Analysis; Investigator Visit Reports (IVR) for Site #3456 (Syan) and #3583 (Korban), Test Article Accountability and Shipment Records of terminated sites.

**b. General observations/commentary:** At the close of this inspection a 3-item FDA 483 was issued for:

- 1) An investigator who did not comply with the signed agreement, general investigational plan was not terminated;
- 2) Failure to ensure proper monitoring and ensure the study is conducted in accordance with the investigational plan; and
- 3) Drug shipments were not discontinued after the investigator's participation in the study was terminated for noncompliance. Specific findings included the following:

**Observation 1:** For Site #3456 (Gurcharan Syan), monitoring reports documented poor protocol and compliance issues on numerous occasions. For example, the IVR dated February 17, 2009 noted missing source worksheets for many subjects, missing visit dates and missing subject initials, inconsistencies between source documents and CRF, and poor documentation practices – at least five subjects did not sign the most recent ICD at their latest visit. The Inspection Visit Report (IVR) of June 23, 2009 and July 20, 2009 noted ECG's not signed by the PI for several subjects, and baseline, 30-day, 4 and 8- month laboratory reports signed, often several months later after receipt from the lab. The IVR of November 25, 2009 noted that one subject had an endpoint event (angioplasty) on November 19, 2009 that was not reported.

**Observation 2:** For Site #3583 (Elie Korban), the IVR of December 12, 2007 noted two locations listed on the Form FDA 1572 that were enrolling subjects: Lexington, TN was listed as the main site, and Jackson, TN was listed as the satellite site. The IVR of May 7, 2008 noted that only the Lexington, TN was involved in the study, and the Jackson, TN location was not involved in the study; the IVR of December 3, 2008 noted that all study supplies had been moved to the Jackson, TN location for the remainder of the trial. The IVR of September 21, 2010 documented that about 15% of subjects were seen at the Lexington, TN location, and lab supplies are brought by the study coordinator from the Jackson site and returned for processing and shipping. The IVR of March 11, 2009 stated that the SC was to provide a Note to File describing the move to the Jackson, TN site, and to the transfer of investigational product between the two sites.

**Observation 3:** Site #3591 (Makam) received the Investigational Medicinal Product (IMP) on June 8, 2011 after being terminated by the sponsor for non-compliance on April 18, 2011. The IMP was reported destroyed on June 16, 2011.

MSD provided a written response to the above observational findings in a letter dated January 14, 2014. Concerning Observation 1, MSD disagreed that the issues at Dr. Syan's site warranted termination at the site, stating that these deficiencies did not jeopardize the primary efficacy outcome or patient safety, and that Dr. Syan implemented a comprehensive Corrective and Preventative Action Plan (CAPA) following a sponsor GCP site audit conducted in February 2009, where similar issues were identified. Further, MSD states that they continue to

work closely with Dr. Syan's site to help maintain GCP compliance. Concerning Observation 2 and 3, MSD outlined a corrective action plan to ensure these actions do not occur in the future. OSI considers the response acceptable.

**c. Assessment of data integrity:** Although the inspection of the Sponsor (MSD) found sporadic instances in which the sponsor failed to ensure proper monitoring and ensure the study is conducted according to the protocol, where drug shipments to an investigator site were not discontinued after the investigator was terminated, the issues are minor, and unlikely to impact data integrity. OSI recommends that the data be accepted in support of the studies conducted under this NDA.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four foreign and one domestic clinical investigator inspections and a Sponsor site inspection where clinical records were maintained, were conducted in support of NDA 204886. No regulatory violations were found during the inspections of Dr. Burgess (South Africa) and Dr. Korban (U.S.). Both inspections were classified as NAI. Minor regulatory violations were found during the inspections of Dr. Bar (Czech Republic), Dr. Syan (Canada), and Dr. Friedrich (Brazil), and a one observational Form FDA 483 was issued for failure to follow the investigational plan. The sponsor site inspection yielded a 3-observational FDA 483 for failure to ensure proper monitoring, follow the investigational plan and not discontinuing drug shipments to a site that had been discontinued due to GCP noncompliance.

Although regulatory violations were noted at Dr. Bar, Dr. Syan, Dr. Friedrich and sponsor sites as described above, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data from this study may be considered reliable.

**Note:** The final EIRs for Drs. Friedrich, Bar, and Syan were not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARON K GERSHON  
03/14/2014

SUSAN D THOMPSON  
03/20/2014

KASSA AYALEW  
03/20/2014

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**LABEL AND LABELING REVIEW**

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

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

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**Date of This Review:** February 12, 2014  
**Requesting Office or Division:** Division of Cardiovascular & Renal Products (DCRP)  
**Application Type and Number:** NDA 204886  
**Product Name and Strength:** Zontivity (voraxapar) tablets, 2.08 mg  
**Product Type:** Single- ingredient product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Merck Sharp & Dohme Corp.  
**Submission Date:** May 10, 2013  
**OSE RCM #:** 2013-1568  
**DMEPA Primary Reviewer:** Janine Stewart, Pharm D.  
**DMEPA Team Leader:** Lisa Khosla, PharmD, MHA

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**1. REASON FOR REVIEW**

This review evaluates the proposed labels and labeling for Zontivity (voraxapar) for areas of vulnerability that could lead to medication errors in response to a request from the Division of Cardiovascular & Renal Products (DCRP).

**2. MATERIALS REVIEWED**

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

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

N/A=not applicable for this review

**3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED**

We performed a risk assessment of the proposed full prescribing information, container labels, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement. We noted that the presentation of the container labels and carton labeling of Zontivity are consistent with the Applicant’s optimized packaging design for solid oral drug products. Additionally, the most recent review of the quarterly monitoring report on the optimized packaging design (OSE Review # 2014-99) did not identify any potential concerns with the optimized packaging design. However, we noted that the presentation of the established name is less than ½ the proprietary name on the sample blister card label and carton labeling. Therefore, we provide a recommendation in Section 4 to improve the prominence of the established name commensurate to the proprietary name.

#### **4. CONCLUSION & RECOMMENDATIONS**

DMEPA concludes that the proposed label and labeling align with the current optimized packaging design. However, the sample blister card label and carton labeling can be improved to increase the readability and prominence of important information.

##### **4.1 RECOMMENDATIONS FOR THE APPLICANT**

###### **A. General Comment**

1. Ensure that the established name is at least  $\frac{1}{2}$  the size of the proprietary name on all labels and labeling, taking into account all pertinent factors including typography, layout, contrast and other printing features as per 21 CFR 201.10(g)(2).

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zontivity that Merck Sharpe & Dohme Corp. submitted on May 10, 2013. An amendment was submitted on January 3, 2014 to amend the product strength expression.

Table 2. Relevant Product Information for Zontivity	
Active Ingredient	Voraxapar
Indication	For the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI).
Route of Administration	Oral
Dosage Form	Tablets
Strength	2.08 mg voraxapar (equivalent to 2.5 mg voraxapar sulfate)
Dose and Frequency	2.08 mg orally once daily, with or without food
How Supplied	NDC 0006-0351-31 bottles of 30 tablets NDC 0006-0351-54 bottles of 90 tablets NDC 0006-0351-48 unit dose packages of 100 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F); excursion permitted to 15°C to 30°C (59°F to 86°F). Store tablets in the original package with the bottle tight
Container Closure	Unit dose blister consists of clear (b) (4) blisters with (b) (4) aluminum foil; White opaque high density polyethylene (HDPE) bottles with a (b) (4) seal. Tamper evident tape may be placed over the closures.

### APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) - N/A

## **APPENDIX C. PREVIOUS DMEPA REVIEWS**

### **C.1 Methods**

We searched the L: Drive on January 3, 2014 using the terms, Zontivity and Voraxapar to identify reviews previously performed by DMEPA. We also used the term “Merck” to identify any reviews we previously performed on Merck’s bundle label and labeling design.

### **C.2 Results**

The search yielded two DMEPA Proprietary Name Reviews. The first was completed on August 9, 2013 under OSE RCM# 2013-1197 in which the proprietary name, Zontivity, was found acceptable. The second was completed on January 24, 2014 under OSE RCM# 2014-16772 in response to Merck Sharp and Dohme’s re-submission of the proposed proprietary name, Zontivity, due to a change in the product’s expression of strength.

Additionally, the search yielded eight Merck Bundle Label and Labeling Postmarketing Commitment reviews. The most recent review was under OSE RCM# 2014-99 dated January 31, 2014.

## **APPENDIX D. HUMAN FACTORS STUDY- N/A**

## **APPENDIX E. ISMP NEWSLETTERS- N/A**

## **APPENDIX F. OTHER- N/A**

## **APPENDIX G. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE**

### **G.1 List of Label and Labeling Reviewed**

We reviewed the following Zontivity labels and labeling submitted by Merck Sharp & Dohme Corp. on January 3, 2014.

- Container label
  - 30-count bottle
  - 90-count bottle
  - Professional sample blister card
  - Unit dose blister card
  
- Carton labeling
  - Sample card carton
  - Unit dose blister carton

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANINE A STEWART  
02/14/2014

LISA V KHOSLA  
02/14/2014

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204886

Application Type: New NDA/NME

Name of Drug: ZONITIVITY (vorapaxar sulfate) Tablets

Applicant: Merck & Co.

Submission Date: 10 May 2013

Receipt Date: 10 May 2013

## 1.0 Regulatory History and Applicant's Main Proposals

Please see RPM Filing Review for regulatory history information regarding this submission.

## 2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

1. The title of the Boxed Warning of the Highlights is not centered.
2. Sponsor noted, (b) (4)  
Sponsor will be ask to edit as follows, "'TRADEMARK is an antagonist of the protease-activated receptor-1 (PAR-1) indicated..".
3. "**WARNING: BLEEDING RISK**" is missing from the TOC, between "Full Prescribing Information" and Section 1.
4. In Section 6.1, Clinical Trials Experience, the sponsor did not use the standard CFR statement and did not place it first in the section.

In addition, the following labeling issues were identified:

1. Per 21 CFR 201.57, since there are no studies in the pediatric patient population, subsection 8.4 should read as follows verbatim:

"Safety and effectiveness in pediatric patients have not been established"

## **RPM PLR Format Review of the Prescribing Information**

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by 15 August 2013. The resubmitted PI will be used for further labeling review.

## 4.0 Appendix

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### Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

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### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

## Selected Requirements of Prescribing Information (SRPI)

Comment:

**YES**

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

#### Highlights Limitation Statement

**YES**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

Comment:

#### Initial U.S. Approval

**YES**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

## Selected Requirements of Prescribing Information (SRPI)

### Boxed Warning

- YES** 12. All text must be **bolded**.  
**Comment:**
- NO** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).  
**Comment:** *Statement not centered.*
- NO** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.  
**Comment:** *Statement is missing, but not needed as box in the HL is identical to the one in FPI.*
- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)  
**Comment:**
- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).  
**Comment:**

### Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.  
**Comment:**
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.  
**Comment:**
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.  
**Comment:**
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).  
**Comment:**

### Indications and Usage

- NO** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”  
**Comment:** *Statement includes additional language.*

## Selected Requirements of Prescribing Information (SRPI)

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

---

## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

## Selected Requirements of Prescribing Information (SRPI)

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.  
Comment: "WARNING: BLEEDING RISK" is missing from the TOC
- NO** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.  
Comment: See above (should be bolded)
- YES** 32. All section headings must be **bolded** and in UPPER CASE.  
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.  
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.  
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "\*Sections or subsections omitted from the Full Prescribing Information are not listed."  
Comment:

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "FULL PRESCRIBING INFORMATION".  
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.  
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>

## Selected Requirements of Prescribing Information (SRPI)

<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

**YES**

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

**YES**

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

**N/A**

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

**YES**

42. All text is **bolded**.

**Comment:**

**YES**

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

**YES**

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

**N/A**

45. If no Contraindications are known, this section must state “None”.

## Selected Requirements of Prescribing Information (SRPI)

### Comment:

#### Adverse Reactions

- NO** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

Comment: Sponsor does not use the text verbatim.

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

Comment:

#### Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALISON L BLAUS  
06/27/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 204886 BLA# n/a	NDA Supplement #:S- n/a BLA Supplement # n/a	Efficacy Supplement Type SE- n/a
Proprietary Name: ZONTIVITY Established/Proper Name: vorapaxar sulfate Dosage Form: Tablets Strengths: 2.5 mg		
Applicant: Merck Agent for Applicant (if applicable): n/a		
Date of Application: 10 May 2013 Date of Receipt: 10 May 2013 Date clock started after UN: n/a		
PDUFA Goal Date: 10 May 2014	Action Goal Date (if different): n/a	
Filing Date: 9 July 2013	Date of Filing Meeting: 14 June 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 - NME		
Proposed indication(s)/Proposed change(s): Secondary prevention of MI		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ): n/a				
List referenced IND Number(s): 71384				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p><b>X</b></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p><b>X</b></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p><b>X</b></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p><b>X</b></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p><b>X</b></p>																		

<b>Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>				
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  <b>If yes, # years requested:</b> FIVE  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDAs/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including:	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			X	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	This is an electronic NDA.
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be</i>	X			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			PERC scheduled for 20Nov13.
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
<b>BPCA (NDAs/NDA efficacy supplements only):</b> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X			
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		<b>X</b>		
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> EoP2 Meeting on 7Feb07	<b>X</b>			EoP2 Minutes dated 16Mar07
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> Pre-NDA Meeting on 19Jun12 and Topline Meeting on 25Apr12	<b>X</b>			Pre-NDA Minutes dated 2Jul13; Topline Minutes dated 21May13
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> n/a		<b>X</b>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 14 June 2013

**NDA #:** 204886

**PROPRIETARY NAME:** ZONTIVITY

**ESTABLISHED/PROPER NAME:** vorapaxar sulfate

**DOSAGE FORM/STRENGTH:** 2.5 mg Tablets

**APPLICANT:** Merck & Co.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

**Patients with History of Myocardial Infarction (MI)**

TRADEMARK (vorapaxar sulfate), an antagonist of the protease-activated receptor-1 (PAR-1), is indicated for the reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). TRADEMARK has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).

**BACKGROUND:** Vorapaxar, or SCH 530348, is an antagonist of the protease-activated receptor-1 (PAR-1) that inhibits thrombin-induced platelet aggregation. The applicant conducted two P3 trials:

- **TRA-CER** - A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 530348 in Addition to Standard of Care in Subjects With Acute Coronary Syndrome. Patients in this trial were either randomized to placebo or 40mg loading dose of vorapaxar followed by a daily maintenance dose of 2.5mg.
- **TRA 2P/TIMI 50** - a multinational, multicenter, double blind trial to evaluate the efficacy and safety of vorapaxar in addition to standard of care, compared to placebo in addition to standard of care in the secondary prevention of ischemic events in patients with established atherosclerotic disease, as manifested by coronary artery disease (CAD), cerebrovascular disease (CVD) or peripheral arterial disease (PAD). The primary endpoint in this trial was the reduction in the incidence of cardiovascular death, myocardial infarction (MI), stroke and urgent coronary revascularization relative to standard of care alone. Patients in 2P were randomized to receive either 2.5 mg daily of vorapaxar or matching placebo.

TRACER was stopped for an unacceptably increased risk of intracranial hemorrhage in subjects taking vorapaxar. Based on those results, subjects in TIMI 50 with a previous history were immediately discontinued from study drug.

We met with the applicant on two occasions to discuss this dossier. The first was a topline meeting to discuss the results from the P3 trials TRACER/TRA-2P on 25Apr12

(minutes dated 21May12) and the second was a pre-NDA meeting on 19June12 (Minutes dated 2July2012).

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Alison Blaus	Y
	CPMS/TL:	Edward Fromm	N
Cross-Discipline Team Leader (CDTL)	Tom Marciniak		N
Clinical	Reviewer:	Martin Rose Jonathan Levine	Y Y
	TL:	Shari Targum	N
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Clinical Pharmacology	Reviewer:	Sudharshan Hariharan Fang Li (Pharmacometrics) Hobart Rogers (Genomics)	Y Y N
	TL:	Raj Madabushi Yanning Wang (Pharmacometrics) Michael Pacanowski (Genomics)	Y N N
Biostatistics	Reviewer:	Yeh-Fong Chen	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Patricia Harlow	Y
	TL:	Tom Papoian	Y
Statistics (carcinogenicity)	Reviewer:	Atiar Rahman	N
	TL:	Karl Lin	N

Immunogenicity (assay/assay validation) (for BLAs/BLA efficacy supplements)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Product Quality (CMC)	Reviewer:	Thomas Wong Okpo Eradiri (Biopharm)	Y
	TL:	Kasturi Srinivasachar Angelica Dorantes (Biopharm)	Y N
Quality Microbiology (for sterile products)	Reviewer:	Erika Pfeiler	Y
	TL:	n/a	n/a
CMC Labeling Review	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Facility Review/Inspection	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OSE/DMEPA (proprietary name)	Reviewer:	Kimberly Defronzo	Y
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:	Danielle Smith	N
	TL:	Reema Mehta	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	N
	TL:	Susan Leibenhaut	N
Controlled Substance Staff (CSS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Other reviewers	Karen Dowdy (Patient Labeling)		Y
Other attendees	Norman Stockbridge (Director), Stephen Grant (Deputy Director), Allen Brinker (OSE), Oanh Dang (OSE-DPVI)		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b> Will be a one day AC, between 14-16 January 2014</p> <p><b>If no, for an NME NDA or original BLA , include the reason. For example:</b></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: 14-16 January 2014 <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:

<i>mitigation, treatment or prevention of a disease</i>	
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>CLINICAL MICROBIOLOGY</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>Comments:</b> Pharmacometrics and Pharmacogenomics also noted that the application was fileable.</p> <ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>BIOSTATISTICS</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b>Comments:</b>	
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b> Biopharm also noted that the application was fileable, but will have issues for the 74-day letter regarding salt-base BE issues and stability.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<u><b>Environmental Assessment</b></u>  <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <b>If no</b>, was a complete EA submitted?   <b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Quality Microbiology (for sterile products)</b></u>  <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDA/NDA supplements only</b>)</li> </ul> <b>Comments:</b> Quality-micro was assigned to the NDA, but their filing review closed out their assignment.	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Facility Inspection</b></u>  <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Facility/Microbiology Review (BLAs only)</b></u>  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>We agreed that they could submit analyses of the primary endpoint, based on the level of financial disclosure obtained in the P3.</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority: Robert Temple, M.D.</b>	
<b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 10 October 2013	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74

<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALISON L BLAUS  
06/24/2013