

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204886Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: February 19, 2014

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Drug Name(s): Zontivity (vorapaxar sulfate)

Therapeutic Class: Antiplatelet

Dosage and Route: 2.5 mg oral tablets

Application Type/Number: NDA 204886

Applicant/sponsor: Merck

OSE RCM #: 2013-1170

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review documents the Division of Risk Management's evaluation of the proposed Risk Evaluation and Mitigation Strategy (REMS) for New Drug Application (NDA) 204886 for Zontivity (vorapaxar sulfate) tablets. The proposed REMS, voluntarily submitted by Merck and received on May 10, 2013 as part of the original NDA submission has the goal of communicating to healthcare providers the risk of serious bleeding, including intracranial hemorrhage (ICH), associated with Zontivity and the need for appropriate patient selection. The proposed REMS consists

(b) (4)

1.1 BACKGROUND

Vorapaxar sulfate is an inhibitor of the PAR-1 receptors on platelets which are activated by thrombin. The proposed indication is reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). The proposed dose is 2.5 mg by mouth daily. Currently, patients indicated for treatment are prescribed other anti-thrombotic products in addition to aspirin and/or clopidogrel. Other platelet inhibitor drugs include Effient (prasugrel), Brilinta (ticagrelor), Xarelto (rivaroxaban), Eliquis (apixaban), and Pradaxa (dabigatran). The other products in the class were all approved with a REMS (communication plans (CP) and/or medication guide) to address the serious risk of severe bleeding. All these products whose REMS have been assessed to date showed adequate prescriber knowledge of the risk of bleeding associated with the class of products and were subsequently released from the REMS requirement.¹ The risk of severe bleeding is ubiquitous to the class.

1.2 REGULATORY HISTORY

- May 10, 2013: NDA 204886 submitted. It was granted a standard review with a user fee goal date of May 10, 2014, and is being evaluated under the PDUFA V program.
- October 31, 2013: Midcycle Communication Meeting held with Sponsor. DRISK communicated to the sponsor that, at this time, a REMS would not be necessary for approval of their product.
- January 15, 2014: A meeting of the Cardiovascular and Renal Drugs Advisory Committee was held to discuss vorapaxar. The Committee voted 10-1 in favor of approval.

¹ The REMS for the following antiplatelet drugs have been released: Brilinta (10/2013), Effient (3/2012), Pradaxa (4/2011), Xarelto (2/2014). Eliquis was approved in December 2012 and is not due to submit its first REMS assessment until June 2014.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Merck: Proposed Risk Evaluation and Mitigation Strategy received May 10, 2013
- Merck: REMS Supporting Document received May 10, 2013
- Merck: Draft Prescribing Information for vorapaxar

2.2 MATERIALS INFORMING THE REVIEW

- Triocci, P., Huang, Z., Held, C., et.al. Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes. *New England Journal of Medicine*. (2012): 366: 20-32.
- Morrow, D., Braunwald, E., Bonaca, M., et.al. (2012). Vorapaxar in the Secondary Prevention of Atherothrombotic Events. *New England Journal of Medicine*. (2012): 366: 1404-1413
- Primary Clinical Review. M. Rose, MD. December 16, 2013
- Vorapaxar AC Briefing Book. January 9, 2014.

3 RESULTS OF REVIEW OF PROPOSED ZONTIVITY RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM

Two pivotal studies were completed for vorapaxar sulfate.

- The TRA 2°P trial- A global placebo-controlled, event-driven randomized controlled trial conducted in 26,499 subjects with at least one of the three following atherosclerotic conditions: Prior Myocardial Infarction (MI) or prior ischemic stroke (occurring from 2 weeks to 12 months prior to study entry), or established peripheral arterial disease (PAD). Prior MI patients were to make up 70% of enrolled subjects.
- The TRA-CER trial- A global, multi-center randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Vorapaxar in Addition to Standard of Care (including other antiplatelet agents) in 12,944 subjects with Acute Coronary Syndrome without ST-segment elevation within 24 hours before presentation to the hospital.

The primary efficacy endpoint of the TRA 2°P trial was the composite of death from cardiovascular causes, myocardial infarction, or stroke. The primary endpoint for the TRACER trial was a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with re-hospitalization, or urgent coronary revascularization. Of note, TRACER was terminated early because of an increased rate of major bleeding, including intracranial hemorrhage (ICH) in the vorapaxar arm. Simultaneously, patients with a history of stroke were terminated early in TRA2P. TRA2P continued and was completed with the remainder of the population.

Key Efficacy Findings: In the overall ITT Population in TRA2P, vorapaxar significantly reduced the hazard of the primary composite endpoint of death from cardiovascular causes, myocardial infarction or stroke by 12% (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.82 – 0.95, p=0.001).

3.2 SAFETY CONCERNS

The only substantial safety risk for vorapaxar is the increased risk of bleeding². The overall bleeding risk (for moderate or severe GUSTO bleeding) for the as-treated population was 3.2% compared to a 2.0% event rate with placebo (hazard ratio [HR] 1.67, 95% confidence interval [CI] 1.43 – 1.94, p=< 0.001). This rate is comparable to other anti-platelet medications.

However, among patients with a history of stroke, the rate of ICH in the vorapaxar group was 2.4% compared with 0.9% in the placebo group (p<0.001). These study results are analogous to the prasugrel experience in ACS subjects³. As a result, the TRACER trial was stopped early since patients with a history of prior stroke were at greater risk for ICH. Simultaneously, those patients were discontinued from participation in TRA2P. Of note, the risk of ICH in the proposed patient population (those who have no history of stroke or TIA) is no higher than that of other medications in the same class.

3.3 RISK MANAGEMENT PLAN PROPOSED BY THE SPONSOR

- A risk management plan proposed by the Sponsor consists of: A REMS with the proposed goal of communicating to healthcare providers the risk of serious bleeding, including intracranial hemorrhage (ICH), associated with Zontivity and the need for appropriate patient selection. The REMS includes (b) (4)
- Medication Guide (outside the REMS)
- Appropriate labeling to address the issue of concern and appropriate patient selection. The proposed labeled population excludes patients with a history of stroke, and a boxed warning against use of the product in patients with a history of stroke or TIA.

² Rose, Martin. Vorapaxar Primary Clinical Review. December 16, 2013

³ Rose, Martin. Vorapaxar Primary Clinical Review. December 16, 2013

3.3.1 Proposed labeling to address the issue of concern and appropriate patient selection

Safety Concern	Proposed Labeling
Increased Risk of ICH in patients with history of stroke or TIA	Boxed Warning: Do not use TRADEMARK in patients with a history of stroke, transient ischemic attack (TIA), or intracranial hemorrhage (ICH); [or active pathological bleeding]
	Section 4. Contraindications: TRADEMARK is contraindicated in patients with a history of stroke or transient ischemic attack (TIA) because of an increased risk of intracranial hemorrhage (ICH) in this population.
Risk of Bleeding	Section 5. Warnings and Precautions: Antiplatelet agents, including TRADEMARK, increase the risk of bleeding, including ICH and sometimes fatal bleeding.

4 DISCUSSION

The benefits of treatment with vorapaxar were demonstrated by meeting the primary endpoint of reduction of cardiovascular death in the intention to treat population in TRA2P. The serious risk of severe bleeding associated with vorapaxar is a risk intrinsic to all anti-platelet medications. Therefore, a survival benefit (as demonstrated in the TRA2P trial) in the labeled patient population compared to a relatively low instance of moderate to severe bleeding (3.2%) results in a favorable risk-benefit profile for this medication.

Additionally, it is expected that the prescriber population that is currently responsible for prescribing anti-platelet medications will be the same for vorapaxar, therefore, there will be a baseline familiarity with the management of the risks of this medication class. Furthermore, the anti-platelet medication Effient (prasugrel) which had a REMS that was most similar to that proposed for vorapaxar (i.e. warned of the contraindicated patient population with a history of stroke and TIA), had its REMS released after the REMS assessment showed that 71% of surveyed providers indicated that Effient should be discontinued in patients who experience TIA or stroke⁴. Since the same prescriber

⁴ Cvetkovich, T. Effient REMS Assessment Review. February, 15, 2012.

population is expected for vorapaxar, one could again conjecture that the prescribers are familiar with the risks and appropriate use of these products, and apply the knowledge gained through the Effient REMS regarding the risk of bleeding to managing patients prescribed vorapaxar. Thus, a REMS [REDACTED] ^{(b) (4)} does not appear warranted for vorapaxar.

To mitigate the above risks of bleeding, the Sponsor voluntarily proposed a REMS with a [REDACTED] ^{(b) (4)} labeling which includes a medication guide. After discussion with the Medical Officer in DCaRP, as well as the Deputy Director for Safety, it was agreed that the risk of bleeding and increased risk of ICH in patients with a history of TIA or stroke can be effectively managed with the labeling, that includes a boxed warning and a medication guide. Therefore, the team's recommendation is for this product not to have a REMS at this time.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for vorapaxar at this time. Vorapaxar has proven to have a survival benefit for patients who have suffered an MI who have not had a stroke or TIA. 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, which also has an increased risk of ICH in susceptible patients, has had its communication plan REMS released. Thus, the benefit-risk profile for vorapaxar is favorable and its serious risks can be mitigated through the professional labeling.

Should the Division have any concerns or questions, or feel that a REMS may be warranted for this product after further review, please contact DRISK.

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/s/

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02/19/2014

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