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January 29, 2014

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Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Norman Stockbridge, M.D., Ph.D.
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Office of Drug Evaluation I
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Dear Dr. Woodcock and Dr. Stockbridge:

These comments from Public Citizen's Health Research Group are being sent in response to New Drug Application (NDA) #204886 — submitted by Merck, Sharp & Dohme Corp., Inc., and considered by the Food and Drug Administration's (FDA's) Cardiovascular and Renal Drugs Advisory Committee (CRDAC) on January 15, 2014 — for vorapaxar sulfate (ZONTIVITY). The proposed indication for use for vorapaxar is:[1]

> Reduction of atherothrombotic events in patients with a history of myocardial infarction (MI). ZONTIVITY has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).

We strongly recommend that if the FDA decides to grant approval to the NDA for vorapaxar, the following actions should be taken to ensure patient safety as a condition of approval:

(1) Require that the drug label for vorapaxar include a black box warning indicating that:

[1] Food and Drug Administration. FDA draft briefing document for the Cardiovascular and Renal Drugs Advisory Commmittee (CRDAC) for meeting on January 15, 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM381327.pdf. PDF page 2. Accessed January 25, 2014.

(a) use of the drug is contraindicated in any patient with a prior history of stroke or transient ischemic attack (TIA), regardless of how recently the event occurred, because of the significant risk of drug-induced hemorrhagic stroke; and

(b) use of the drug is contraindicated in patients with a body weight of less than 60 kilograms (kg) because of an unfavorable risk-benefit profile.

(2) Limit the approved indication for use of vorapaxar to patients with a prior history of MI, and do not expand it to include patients who have a history of peripheral artery disease (PAD) but no history of MI.

I. Background

Vorapaxar, a new molecular entity, is a reversible antagonist of the protease-activated receptor-1 (PAR-1).[2] This receptor is found in many cell types, including platelets and vascular endothelial cells.[3] Blocking PAR-1 receptors on platelets inhibits thrombin-mediated platelet aggregation.[4]

The primary data to support approval of vorapaxar for the proposed indication were provided by the TRA 2°P trial, a very large multicenter and multinational randomized, placebo-controlled trial designed to evaluate whether the drug was safe and effective for reducing atherothrombotic events in patients with established atherosclerosis who were simultaneously receiving standard anti-platelet therapy (aspirin and/or a thienopyridine such as clopidrogrel).[5,6] The trial involved 26,499 subjects who had at least one of the following atherosclerotic disorders: prior MI between two weeks and 12 months prior to enrollment, prior ischemic stroke between two weeks and 12 months prior to enrollment, or established PAD.[7] The primary study endpoint was time to a composite of cardiovascular death, MI, stroke, or urgent coronary revascularization, and the key secondary endpoint was time to a composite of cardiovascular death, MI, or stroke.[8]

II. Need for black box warnings

A. Contraindication to use in any patient with a prior history of stroke or TIA

If approved, the drug label for vorapaxar should include a black box warning indicating that use of vorapaxar is contraindicated in any patient with a prior history of stroke or TIA because of the significant risk of hemorrhagic stroke and the lack of clinical benefit in these patients. The need

[2] *Ibid*. PDF page 27.
[3] *Ibid*. PDF page 27.
[4] *Ibid*. PDF page 27.
[5] *Ibid*. PDF page 14.
[6] Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med.* 2012;366(15):1404-1413.
[7] Food and Drug Administration. FDA draft briefing document for the Cardiovascular and Renal Drugs Advisory Commmittee (CRDAC) for meeting on January 15, 2014. PDF page 14. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM381327.pdf. Accessed January 25, 2014.
[8] *Ibid*. PDF page 14.

for such a warning is obvious given the safety and efficacy data from the TRA 2°P trial, and we assume the FDA is already contemplating requiring such a warning.

After completion of enrollment in the TRA 2°P trial and after subject follow-up had reached a median of 24 months, the data and safety monitoring board (DSMB) for the trial reported a substantial excess of intracranial hemorrhage in subjects with a history of stroke randomly assigned to the vorapaxar group [2.4% in the vorapaxar group versus 0.9% in the placebo group, hazard ratio 2.55 (95% confidence interval 1.52 to 4.28), p<0.001].[9] Moreover, there was no observed benefit of vorapaxar for the primary endpoint in the subset of subjects with a prior history of stroke [10.5% in the vorapaxar group versus 10.9% in the placebo group, hazard ratio 0.94 (95% confidence interval 0.80 to 1.10), p=0.465].[10] As a result, the DSMB recommended discontinuation of the trial drug in all subjects with a prior history of stroke, including those with a new stroke during enrollment in the trial. The DSMB recommended that the trial continue for subjects without a history of stroke. These recommendations were implemented by the investigators.

In contrast, with respect to the subset of subjects in the TRA 2°P trial who met the criteria for the proposed label population, the benefits of the drug appeared to outweigh the risks, including the small increased risk of hemorrhagic stroke. For this subgroup of subjects, the primary endpoint occurred in 8.5% of vorapaxar subjects versus 10.3% of control subjects (hazard ratio 0.82, 95% confidence interval 0.74 to 0.90, p<0.001). Hemorrhagic stroke was the qualifying primary endpoint in 0.2% of vorapaxar-treated subjects and 0.1% of control subjects.[11]

The FDA asked the CRDAC whether the sponsor's proposed restriction on the use of vorapaxar with respect to a prior history of stroke or TIA should be limited to some specified time interval following a patient's most recent stroke. This question resulted from an analysis of the effect of the timing of prior history of stroke (considering the most recent stroke) on the key secondary endpoint in subjects with a prior history of stroke who were enrolled in the 2°P trial (see the table below, excerpted from the FDA briefing materials).[12] The data suggested a trend toward a net harm from vorapaxar for the key secondary endpoint for subjects whose most recent stroke occurred within six months prior to randomization, but they showed a trend toward net benefit for those subjects whose most recent stroke occurred more than six months prior to randomization.

[9] Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med.* 2012;366(15):1404-1413.
[10] Food and Drug Administration. FDA draft briefing document for the Cardiovascular and Renal Drugs Advisory Commmittee (CRDAC) for meeting on January 15, 2014. PDF page 16. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM381327.pdf. Accessed January 25, 2014.
[11] *Ibid*. PDF page 17.
[12] *Ibid*. PDF page 110.

Table 49 Effect of Timing of Prior Stroke on Rate of Key Secondary Endpoint [1]
Subjects in CVD (prior stroke) stratum, stratified by time of most recent stroke to randomization

Time from most recent stroke to randomization	Placebo		Vorapaxar		V vs. P HR (95% CI)	p
	n/J (%)	KM%	n/J (%)	KM%		
< 3 months	107/1243 (8.6)	11.9%	115/1255 (9.2)	14.4%	1.06 (0.82 – 1.38)	0.66
3 to 6 months	55/733 (7.5)	9.9%	62/706 (8.8)	13.8%	1.20 (0.83 – 1.72)	0.33
> 6 months	45/442 (10.6)	14.7%	31/446 (7.0)	10.1%	0.67 (0.43 – 1.06)	0.09

1 Time to first event of composite of CV death, MI and stroke
Source: Applicant's KM curves with annotations, Figures E-2.18 to E-2.20 (without data on nature of event)

Regarding these data, the FDA medical reviewer noted the following:[13]

> However, there are reasons to be skeptical of the seemingly beneficial profile of vorapaxar in those with their most recent stroke more than 6 months prior to randomization. This subgroup is considerably smaller than the others, and even though the [hazard ratio] for the Key Secondary Endpoint was 0.67 in this subgroup, the 95% CI was wide and crossed 1.0. In addition, the rate of events in the placebo arm of this timing subgroup was higher than either of the other two timing subgroups. This is the opposite of what one would expect and is inconsistent with the vorapaxar arm data, which show a step-wise reduction in the event rate as the time from prior stroke to randomization increases, rather than the "V" shaped pattern in the placebo arm.
>
> Finally, the data from the TRITON-TIMI 38 trial of prasugrel vs. clopidogrel in subjects with [acute coronary syndrome] raise concerns. That study showed an increased rate of stroke in subjects in the prasugrel arm compared to control in the subset of subjects with a prior history of stroke. The data for timing of the prior event with respect to randomization (which was a binary choice on the CRF: either less than one year prior or ≥ 1 year prior) suggest that the increased relative risk of stroke with prasugrel vs. control (about 3.5 to 1) was similar in those with prior stroke < 1 year before randomization and those with prior stoke ≥ 1 year before randomization, although the absolute rates of stroke in both arms were higher in those with more recent prior stroke and the total number of strokes in the prior stroke population was small (14). This relationship may also hold for vorapaxar, even though vorapaxar and prasugrel affect different receptors on platelets and the populations in TRITON and TRA 2°P differed.
>
> > *Reviewer comment: Given the factors noted above, it seems prudent to assume that the risk of [cardiovascular] events in subjects with a prior history of stroke treated with vorapaxar may remain elevated even if the most recent stroke was more than 6 months prior to the start of treatment.*

[13] *Ibid*. PDF pages 110-111.

We strongly agree with the FDA medical reviewer's assessment. The use of vorapaxar should be contraindicated in any patient with a prior history of stroke or TIA, regardless of when the most recent stroke or TIA occurred.

Given the increased risk of hemorrhagic stroke in patients with prior history of stroke, the devastating nature of such events, and the lack of demonstrated benefit in this subpopulation, a black box warning is clearly warranted.

B. Contraindication to use in any patient weighing less than 60 kg

If approved, the drug label for vorapaxar should include a black box warning also indicating that use of the drug is contraindicated in patients with a body weight of less than 60 kg because data from the TRA 2°P trial demonstrated an unfavorable risk-benefit profile in this subpopulation of patients. The following analysis and discussion by the FDA pharmacology reviewers strongly support the need for such a warning:[14]

> The increased drug exposure in lighter patients and the exposure-bleeding relationship provided a clear pharmacological justification to look into the safety subgroup analysis based on body weight. A subgroup analysis of the overall population from TRA2°P - TIMI 50 for GUSTO severe or moderate bleeding events showed that the hazard ratio between vorapaxar and placebo was 1.87 [95% CI: 1.19-2.94] in patients with body weight < 60 kg while it was estimated to be 1.48 [95% CI: 1.28-1.73] in patients with body weight ≥ 60 kg patients. The larger point estimate of HR for the lighter patients suggested that the increased bleeding risk of vorapaxar relative to placebo was even higher [87%] in lighter patients when the hazard of bleeding was already 48% higher for vorapaxar relative to placebo in heavier patients…
>
> Given the increased risk of bleeding in patients with body weight < 60 kg, a reasonable benefit on the efficacy endpoint should be demonstrated to justify the increased bleeding risk from a risk/benefit perspective. However, the weight based subgroup analysis for the efficacy endpoint showed that vorapaxar was almost statistically worse than placebo with a HR of 1.28 [95% CI: 0.95-1.73] in the overall population.
>
> To explore whether the results for the weight based subgroup analyses were due to chance, a resampling procedure was used to randomly select 1852 patients from the overall population of 26449 [ITT population] with a randomization allocation of 1:1 between placebo and vorapaxar arms [926 per arm]. The hazard ratio of the randomly selected subgroups [vorapaxar relative to placebo] was calculated. Such a procedure was repeated 100,000 times to evaluate the chance of estimating a hazard ratio of 1.28 or larger when the hazard ratio was 0.88 between the two arms in the overall population. The random chance of generating a subgroup [N=1852] with a hazard ratio of 1.28 or larger was estimated to be 0.0057, suggesting the results for the weight based subgroup analyses were unlikely due to random chance…

[14] *Ibid.* PDF pages 243-246.

The applicant's rationale to use 60 kg as the cutoff was based on precedent set by product labeling for other anti-platelet agents. Further analyses were conducted to explore different cutoff values. Figure 9 shows that 60 kg is a reasonable choice to identify a subgroup with no clear benefit on the efficacy endpoint.

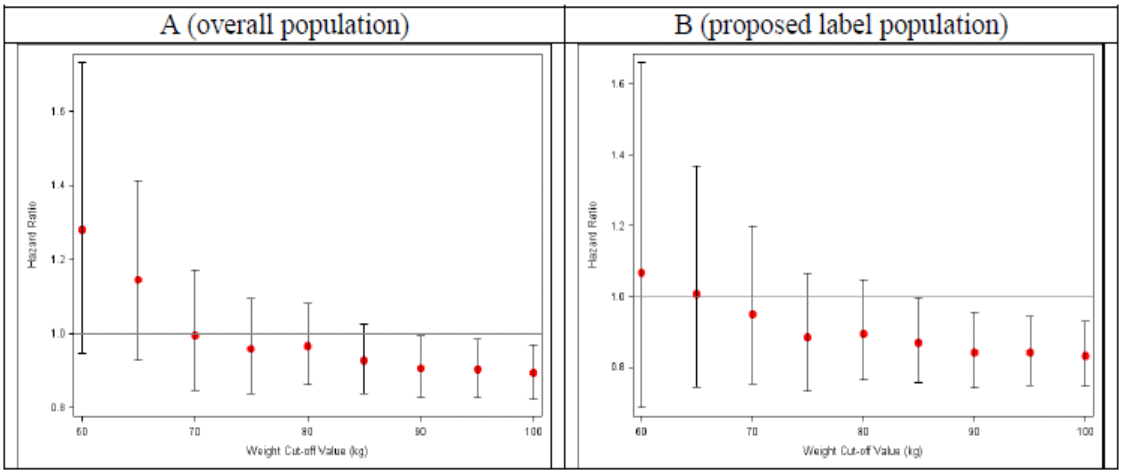

Figure 9: Hazard ratio of efficacy endpoint between vorapaxar and placebo for a subgroup based on different body weight cutoff values. Each dot represents the hazard ratio for subgroup of patients with body weight < cut-off value [error bars represent the 95% CI]

Prior stroke was considered the most important risk factor for intracranial hemorrhage by the data safety monitoring board [DSMB] and was the first exclusion criterion applied by the applicant to limit the patient population to achieve a favorable risk/benefit balance. However, the body weight based subgroup analyses suggested that the similar risk/benefit could be achieved by excluding patients with body weight < 60 kg [Table 8].

Table 8: Comparison of efficacy and safety results based on two different subgroups

Endpoint	Subgroup	Hazard Ratio [95% CI]	Total sample size
Efficacy	Post MI and ≥60 kg	0.82 [0.74-0.90]	16836
	Post MI and no prior stroke/TIA	0.82 [0.74-0.90]	16897
GUSTO severe or moderate bleeding	Post MI and ≥60 kg	1.45 [1.18-1.77]	16795
	Post MI and no prior stroke/TIA	1.48 [1.21-1.82]	16856

Based on their analysis, the FDA pharmacology reviewers made the following recommendation:[15]

> **Avoid use of vorapaxar in patients with body weight < 60 kg due to unfavorable benefit-risk.** [Emphasis added]

We strongly agree with the FDA pharmacology reviewers' recommendation. A contraindication to use in patients weighing less than 60 kg should be placed in a black box warning, as physicians and pharmacists may not routinely take patient weight into account when initiating therapy, especially in the acute setting, unless alerted with a prominently placed warning.

III. The proposed indication for vorapaxar should not be expanded to include PAD as suggested by the FDA

Based on a subgroup analysis from the TRA 2°P trial, the sponsor's proposed indication for vorapaxar use is limited to patients with a prior history of MI. The FDA, however, has suggested that the indication for use could be expanded to include patients with a history of PAD and has requested from the sponsor more detailed risk and benefit data on this subgroup.[16]

We strongly disagree with the FDA's suggestion and urge the agency to limit any approved indication for use of vorapaxar to patients with a prior history of MI, as proposed by the sponsor. The indication should not expand to include patients who have a history of PAD but no history of MI because the TRA 2°P trial did not demonstrate a statistically significant reduction in the primary composite endpoints in PAD subjects [12.3% in the vorapaxar group versus 12.9% in the placebo group, hazard ratio 0.95 (95% confidence interval 0.79 to 1.14), p=0.567] or in PAD subjects without a history of stroke or TIA who received vorapaxar in comparison to control subjects [10.9% in the vorapaxar group versus 12.5% in the placebo group, hazard ratio 0.87 (95% confidence interval 0.71 to 1.06), p=0.167].[17] Given the lack of definitive evidence of benefit in PAD patients and the known risk of serious bleeding, including hemorrhagic strokes, a favorable risk-benefit profile has not been established for vorapaxar in such patients.

IV. Conclusions

In conclusion, we strongly recommend that if the FDA decides to grant approval to the NDA for vorapaxar, the following actions should be taken to ensure patient safety as a condition of approval:

(1) Require that the drug label for vorapaxar include a black box warning indicating that:

   (a) use of the drug is contraindicated in any patient with a prior history of stroke or TIA, regardless of how recently the event occurred, because of the significant risk of drug-induced hemorrhagic stroke; and

[15] *Ibid.* PDF page 225.
[16] *Ibid.* PDF page 106.
[17] *Ibid.* PDF page 16.

(b) use of the drug is contraindicated in patients with a body weight of less than 60 kg because of an unfavorable risk-benefit profile.

(2) Limit the approved indication for use of vorapaxar to patients with a prior history of MI, and do not expand it to include patients who have a history of PAD but no history of MI.

Thank you for considering our comments on this very important matter.

Sincerely,

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