

Vorapaxar (ZONTIVITY) National Drug Monograph February 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information¹

Description/Mechanism of Action	Vorapaxar is a first in class platelet inhibitor that acts as an antagonist of the protease activated receptor 1 (PAR-1). PAR-1 is the primary receptor for thrombin-mediated activation of platelets. Vorapaxar may be effective in the treatment of atherothrombotic cardiovascular disease through inhibition of thrombin-mediated platelet aggregation.
Indication(s) Under Review in this document (may include off label)	Vorapaxar is indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD).
Dosage Form(s) Under Review	Vorapaxar 2.08 mg oral tablet (equivalent to 2.5 mg vorapaxar sulfate)
REMS	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS <input type="checkbox"/> Postmarketing Requirements <i>See Other Considerations for additional REMS information</i>
Pregnancy Rating	Pregnancy Category B; further explanation is detailed in Special Populations

Executive Summary

Efficacy	<ul style="list-style-type: none"> Efficacy of vorapaxar for the FDA labeled indication was established in the TRA 2P trial, a large, multinational, placebo controlled, phase 3 study that evaluated over 26,000 patients and followed for a median of 30 months. In high risk patients with a history of MI (2 weeks to 12 months post-MI), ischemic stroke, or PAD, who were on background antiplatelet therapy, vorapaxar was shown to provide a modest but statistically significant reduction in the composite endpoint of cardiovascular death, MI, or stroke compared to placebo. However, a substantial increase in intracranial hemorrhage (ICH) events in the subgroup of patients with a history of stroke or transient ischemic attack (TIA) was found, and there was no observed benefit in the primary endpoint in this group. When patients with a history of stroke or TIA were excluded from the efficacy analyses, the benefit of vorapaxar remained. As a result, FDA approved vorapaxar in patients with a history of MI or PAD only, with a contraindication in the label for patients with history of stroke, TIA, or ICH. In the post-MI cohort of the TRA 2P trial (67% of population), there was a statistically significant reduction in the primary composite endpoint driven by reductions in cardiovascular death and stroke. In the small subgroup with PAD as the qualifying diagnosis for the TRA 2P trial (14%), vorapaxar was not found to significantly reduce primary efficacy events (composite of cardiovascular death, MI, or stroke) compared to placebo, though the study was not adequately powered to detect a difference. There was a statistically significant reduction in the secondary endpoint of acute limb ischemic (ALI) events including related hospitalization and revascularization in patients with PAD. Vorapaxar was also evaluated in a high risk non-ST elevation (NSTE) acute coronary syndrome (ACS) population in the large, multinational, placebo-
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	<p>controlled, phase 3 TRACER trial. This study failed to find a significant benefit and was terminated early due to a significant excess in major bleeding events, including over a 3-fold increase in ICH with vorapaxar.</p>
Safety	<ul style="list-style-type: none"> • Data for the FDA safety review of vorapaxar included a total of 21,630 vorapaxar-treated subjects and was primarily based on two phase 3 studies, TRA 2P and TRACER. The main concern with vorapaxar is bleeding, and the FDA analysis focused on the TRA 2P study where subjects were followed for a median of 30 months. • Vorapaxar was shown to increase bleeding risk across various general bleeding endpoints including the primary safety endpoint of GUSTO moderate or severe bleeding. • In patients with a prior ischemic stroke or TIA, vorapaxar was associated with a significantly increased risk of ICH compared to placebo, and there was no benefit in efficacy outcomes. Therefore, vorapaxar is contraindicated in patients with history of stroke or TIA. • When patients with history of stroke or TIA were excluded (FDA labeled population), GUSTO moderate or severe bleeding rates remained significantly higher with vorapaxar vs. placebo. An excess of ICH and fatal events were observed with vorapaxar, but the differences between the vorapaxar and placebo groups were not statistically different. • Boxed Warning – Bleeding Risk: <ul style="list-style-type: none"> ○ Do not use vorapaxar in patients with a history of stroke, TIA, or ICH or in patients with pathological bleeding. ○ Antiplatelet agents including vorapaxar increase the risk of bleeding.
Other Considerations	<ul style="list-style-type: none"> • Pharmacodynamics: At recommended doses, vorapaxar achieves $\geq 80\%$ inhibition of TRAP-induced platelet aggregation within one week of treatment. Given the long half-life of vorapaxar, 50% of TRAP-induced platelet aggregation inhibition is expected at 4 weeks following discontinuation. • Overdose/Reversal: There is no known treatment to reverse the effects of vorapaxar. Effects on inhibition of platelet aggregation are expected to last for weeks upon discontinuation of vorapaxar, given its long half-life. Dialysis and platelet transfusions are not expected to provide a benefit. • Surgery: With a terminal elimination half-life of 8 days, significant inhibition of platelet aggregation is expected for several weeks following discontinuation of vorapaxar. There are no specific recommendations for management of vorapaxar around surgical procedures provided in the prescribing information. During clinical trials, study investigators were encouraged to continue study drug treatment prior to surgery. In the FDA labeled population (post-MI or PAD patients without TIA or stroke) who underwent CABG surgery, there was a slight excess of major bleeding events and substantially fewer primary endpoint events with vorapaxar compared to placebo. • Storage requirements: Tablets must be stored in original packaging (bottle or blister) until use. Keep bottles tightly closed, and keep the desiccant in the bottle to protect from moisture.
Potential Impact	<p>Projected place in therapy:</p> <ul style="list-style-type: none"> • When added to standard of care (including antiplatelet therapy with aspirin and/or clopidogrel), vorapaxar was shown to provide a modest benefit in reduction of major cardiovascular events compared to placebo in high risk patients with a history of MI. Vorapaxar was associated with a clinically significant increase in major bleeding events. In considering the addition of vorapaxar, individual factors for increased bleeding risk should be weighed against risk of subsequent cardiovascular events. Of note, in the small PAD subgroup (roughly 14% of the total population), vorapaxar was not associated with a statistically significant improvement in the reduction of major cardiovascular events. Vorapaxar was associated with a statistically significant benefit in the reduction of ALI events in

PAD patients at an increased risk of moderate to severe bleeding.

- Vorapaxar is contraindicated in patients with a history of stroke, TIA, or ICH. No benefit and increased bleeding was shown when vorapaxar was added to standard therapy in patients with ACS. When stratified by weight, the small number of patients weighing less than 60 kg appeared to have a less favorable benefit-risk pattern compared to patients with higher body weight.
- The addition of vorapaxar to the standard of care in the management of patients with prior MI or PAD has not yet been addressed in guidelines from the American Heart Association/American College of Cardiology (AHA/ACC). In the 2015 European Society of Cardiology (ESC) Guidelines for the management of NSTEMI ACS, it is recommended to carefully weigh the modest benefit of the addition of vorapaxar to aspirin and clopidogrel against the increase in bleeding events.²
- **Patient convenience:** Vorapaxar is a once daily oral medication that would be added to current therapy (rather than replacing a medication being taken) with the main adverse effect of bleeding.

Background

Purpose for review

Recent FDA approval

Issues to be determined:

- ✓ Evidence of need
- ✓ Does vorapaxar offer advantages to currently available alternatives?
- ✓ Does vorapaxar offer advantages over current VANF agents?
- ✓ What safety issues need to be considered?
- ✓ Does vorapaxar have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Vorapaxar is a novel antiplatelet agent that was studied as add-on therapy to the standard of care (e.g., antiplatelet agents, statins, beta-blockers, ACE-I, etc.) and compared to placebo. It is unclear whether a benefit of vorapaxar monotherapy as an alternative to other antiplatelet therapy exists. There are no comparable therapeutic alternatives.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to February 2016) using the search term <vorapaxar>. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. Randomized controlled Phase 3 trials published in peer-reviewed journals evaluating the FDA approved indication were included. Medical reviews on the FDA web site were also reviewed for additional information.

Review of Efficacy

- FDA approval of vorapaxar was based primarily on the pivotal, phase 3, TRA 2P-TIMI 50 (Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) trial. A second phase 3 study, TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome), provided additional safety information for vorapaxar, though the trial did not meet its primary efficacy outcome in an ACS population. Overall, there is moderate quality evidence supporting the use of vorapaxar in the FDA indicated population of patients with a history of MI or PAD.
- In the TRA 2P trial, vorapaxar was shown to provide a modest reduction in the composite endpoint of cardiovascular death, MI, or stroke compared to placebo in high risk patients with a history of MI, ischemic stroke, or PAD who were on background antiplatelet therapy. However, the subgroup of patients with a history of stroke or TIA were found to have a substantial increase in ICH and no observed benefit in the primary endpoint.¹⁰ When patients with a history of stroke or TIA were excluded from the efficacy analyses, the benefit of vorapaxar remained. As a result, FDA approved vorapaxar in patients with a history of MI or PAD only, with a contraindication in the label for patients with history of stroke, TIA, or ICH.

- In the TRACER trial, vorapaxar failed to show a benefit in reducing the composite endpoint of cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization in a high risk NSTEMI/ACS population. Further, the trial was terminated early due to a significant increase in GUSTO major or moderate bleeding, including over a 3-fold increased risk of ICH.

TRA 2P-TIMI 50³

- The TRA 2P-TIMI 50 study was a multinational, double-blind, placebo-controlled, industry sponsored trial that evaluated the efficacy and safety of the addition of vorapaxar to standard antiplatelet therapy in patients with established atherosclerosis. Patients had to have a history of spontaneous MI or ischemic stroke in the past 2 weeks to 12 months or PAD (defined as history of intermittent claudication in conjunction with either an ankle-brachial index <0.85 or prior revascularization for limb ischemia). By design, the majority of patients enrolled qualified with a history of MI. Notable exclusion criteria were planned revascularization procedures, bleeding diathesis history, recent active abnormal bleeding, concurrent oral anticoagulant therapy, and active hepatobiliary disease.
- Two significant protocol amendments were made during the trial. When the data and safety monitoring board detected an excess of ICH in patients with a history of stroke and receiving vorapaxar (at a median of 24 months of follow-up), study drug was discontinued in all patients with a prior stroke. Secondly, upon review of the TRACER study results evaluating vorapaxar in ACS, the investigators changed the hierarchy of the primary and secondary efficacy endpoints before the study database was locked.
- A total of 26,449 patients were randomized to treatment with 2.5 mg vorapaxar daily or placebo and followed for a median of 30 months. The breakdown of patients by baseline qualifying atherosclerosis event was 67% with MI, 18% with ischemic stroke, and 14% with PAD. Most patients were receiving baseline aspirin (94%) and a lipid lowering agent (91%). The majority of patients with MI were receiving a thienopyridine (nearly all clopidogrel), while only a minority of patients with stroke or PAD were receiving a thienopyridine at baseline.
- At 3 years, vorapaxar was associated with modest, statistically significant improvements in the revised composite primary efficacy endpoint of cardiovascular death, MI, or stroke, mainly driven by reduction in MI (NNT = 83). No statistically significant benefit with vorapaxar was identified for the individual endpoints of cardiovascular death, any cause death, or stroke. The primary composite efficacy endpoint was overall consistent among several subgroups studied, with notable analyses below:

Selected Subgroup analyses

- **Post-MI:** In the 67% of the population with a qualifying MI for study entry, vorapaxar was associated with a statistically significant reduction in the primary composite endpoint of cardiovascular death, MI, or stroke (8.1% vs. 9.7%; HR 0.80; 95% CI 0.72-0.89; $p < 0.0001$), driven mainly by reduction in MI and stroke. No significant reduction in cardiovascular death was observed.⁴
- **PAD:** Compared to the total population, patients with PAD as the qualifying factor for study entry (14% of population; $n = 3,787$) were older and had more baseline co-existing conditions. Most patients were on aspirin and statin therapy at baseline, though fewer patients were receiving a thienopyridine alone (37%) or in combination with aspirin (28%), or cilostazol (11%) in the PAD subgroup. Vorapaxar was not associated with a significant reduction in the primary composite outcome of cardiovascular death, MI, or stroke compared to placebo (11.3% vs. 11.9%; HR = 0.94 [0.78 – 1.14]; $p=0.53$), though there was a statistically significant benefit of vorapaxar in the secondary endpoint of reducing acute limb ischemic (ALI) events including related hospitalization (2.3% vs. 3.9%; HR = 0.58 [0.39-0.86]; $p=0.006$) and revascularization (18.4% vs. 22.2%; HR = 0.84 [0.73-0.97]; $p=0.017$).⁵ The benefit of vorapaxar in reducing ALI events was seen early in treatment (within 30 days) and sustained over time, while the benefit of the drug on reducing the need for peripheral revascularization procedures was not apparent until later in follow-up (greater than 1 year). ALI event results were consistent in patients with any history of PAD and without history of stroke or TIA (FDA labeled population).⁶
- **Ischemic Stroke:** In patients with a prior ischemic stroke as the qualifying factor for study entry (19%; $n = 4,883$), there was non-statistically significant excess of primary outcome events (composite of cardiovascular death, MI, or stroke) with vorapaxar treatment. Further, vorapaxar was associated with a significant increase in bleeding, including ICH. Higher rates of bleeding and ICH were also found in the cohort of patients with qualifying MI or PAD history along with a history of stroke or TIA (see Safety section).⁷ Therefore, use of vorapaxar is contraindicated in patients with a history of stroke or TIA.

- **Advanced age:** Though no significant interaction between age and treatment assignment was observed in TRA2°P, the benefit of vorapaxar appeared to be less in patients 72 years of age and older according to the FDA review.¹⁰ Primary outcome events remained numerically lower in older patients who received vorapaxar compared to placebo, but the difference was no longer statistically significant.
- **Low body weight:** When stratified by weight, the small number of patients weighing less than 60 kg who received vorapaxar appeared to have a less favorable benefit-risk pattern compared to patients with higher body weight (p=0.03 for interaction for efficacy endpoint). Per the FDA review and analysis that investigated data in total from both TRA2°P and TRACER, a consistent reduction in efficacy with vorapaxar in low body weight patients is somewhat unclear, while the increased bleeding seems more consistent across trials.
- **Coronary stents:** In the 55% of the study population with coronary stents (either existing or placed during the study), there was a small but statistically significant and consistent reduction in definite stent thrombosis with vorapaxar vs. placebo (1.1% vs. 1.4%; HR 0.71; 95% CI: 0.51-0.98; p=0.037).⁸

TRA 2P Selected Efficacy Endpoints at 3 years^{1,3}

Efficacy Endpoint	Total Study Population				Patients without TIA or stroke history (FDA labeled indication)			
	VORA N=13,225 %	Placebo 13,224 %	HR (95% CI)	P value	VORA N=10,080 %	Placebo N=10,090 %	HR (95% CI)	P value
1° Endpt: CV death, MI, stroke*	9.3	10.5	0.87 (0.80-0.94)	<0.001	7.9	9.5	0.80 (0.73-0.89)	<0.001
CV death, MI, stroke, or UCR	11.2	12.4	0.88 (0.82-0.95)	0.001	10.1	11.8	0.83 (0.76-0.90)	<0.001
CV death	2.7	3	0.89 (0.76-1.04)	0.15	2.4	2.8	0.86 (0.71-1.03)	Not stated
MI	5.2	6.1	0.83 (0.74-0.93)	0.001	5.4	6.4	0.82 (0.73-0.93)	Not stated
Any stroke	2.8	2.8	0.97 (0.83-1.14)	0.73	1.2	1.6	0.67 (0.52-0.87)	Not stated
Death from any cause	5	5.3	0.95 (0.85-1.07)	0.41	-	-	-	-

CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction; TIA=transient ischemic attack; UCR=urgent coronary revascularization

TRACER⁹

- The TRACER study was a multinational, double-blind, placebo-controlled, industry funded trial that evaluated the efficacy and safety of the addition of vorapaxar to standard therapy in patients with ACS without persistent ST-elevation. Follow-up was terminated early after an unplanned safety review, though the prespecified number of primary outcome events was already reached.
- A total of 12,944 patients were randomized to treatment with a loading dose of 40 mg followed by a daily maintenance dose of 2.5 mg of vorapaxar or matching placebo and followed for a median of 502 days. Though there was a favorable trend, vorapaxar failed to meet its primary composite endpoint in reducing cardiovascular death, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization (18.5% event rate at 2 years with vorapaxar vs. 19.9% event rate with placebo; HR 0.92 [0.85-1.01]; p=0.07). Further, vorapaxar was associated with significantly more bleeding, including over a 3-fold increased risk of ICH.

Potential Off-Label Use

- There may be potential interest in using vorapaxar for various indications such as percutaneous coronary intervention, ACS, and monotherapy in patients who are unable to use other antiplatelet regimens.

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning¹	Bleeding Risk: <ul style="list-style-type: none"> • Do not use vorapaxar in patients with a history of stroke, TIA, or ICH or in

	<ul style="list-style-type: none"> patients with pathological bleeding.
Contraindications¹	<ul style="list-style-type: none"> • Antiplatelet agents including vorapaxar increase the risk of bleeding. • <u>History of stroke, TIA, or ICH</u>: Vorapaxar is associated with an increased risk of ICH in this population. Also, discontinue use in patients who experience a stroke, TIA, or ICH on vorapaxar. • <u>Active pathologic bleeding</u>: Vorapaxar is contraindicated in patients with active pathological bleeding such as ICH or peptic ulcer.
Warnings/Precautions¹	<ul style="list-style-type: none"> • <u>General Risk of Bleeding</u>: <ul style="list-style-type: none"> ○ Antiplatelet agents including vorapaxar increase the risk of bleeding, including ICH and fatal bleeding. ○ Consider the patient's underlying risk of bleeding before starting vorapaxar. Risk factors for bleeding include: older age, low body weight, reduced renal or hepatic function, history of bleeding disorders, concomitant use of medications that increase bleeding risk (e.g., anticoagulants, fibrinolytic therapy, chronic nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors). Avoid concomitant use of vorapaxar and warfarin or other anticoagulants. • <u>Strong CYP3A Inhibitors or Inducers</u>: Avoid concomitant use of vorapaxar and strong CYP3A inhibitors (due to increased vorapaxar exposure) and strong CYP3A inducers (due to decreased vorapaxar exposure) (see Drug Interactions).

Safety Considerations

Data for the FDA safety review of vorapaxar included a total of 21,630 vorapaxar-treated subjects and was primarily based on two phase 3 studies, TRA 2P and TRACER.¹¹ The main concern with vorapaxar is bleeding, and the FDA analysis focused on the TRA2 P study.

Bleeding:

- Across various general bleeding endpoints in the TRA 2P study, vorapaxar was associated with an increased risk of bleeding with hazard ratios ranging from about 1.2 to 1.8 in the as treated (+30 days) population.¹⁰
- For the primary safety endpoint, moderate or severe GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) bleeding occurred in 4.2% of vorapaxar-treated vs. 2.5% of placebo patients at 3 years (HR = 1.66; 1.43 – 1.93; p <0.001; number needed to harm [NNH]=60). Fatal bleeding was rare, though there was a nonsignificant excess of events with vorapaxar.³
- PAD: Similar to the findings in the overall population, in the subgroup of patients with any history of PAD and no history of stroke or TIA (FDA indicated population), GUSTO moderate or severe bleeding rates were significantly higher with vorapaxar vs. placebo (HR = 1.50; 1.14 – 1.98; p=0.003). No apparent increase in ICH or fatal bleeds was observed, though the number of events was small.⁶
- Prior Ischemic Stroke: In patients with a prior ischemic stroke as their qualifying event for study entry, vorapaxar was associated with a 2.5-fold increased risk of ICH compared to placebo (2.5% vs. 1%; p <0.001). GUSTO moderate or severe bleeding was also significantly increased with vorapaxar in these patients, and there was no benefit in efficacy outcomes. Similar increases in ICH were observed in the subgroup of patients with a history of TIA (without known stroke) or stroke who qualified for the study based on MI or PAD (and not stroke). Therefore, vorapaxar is contraindicated in patients with history of stroke or TIA.
- Age: Bleeding increased with increased age independent of treatment assignment with vorapaxar or placebo.
- Low body weight: In the small group of patients weighing less than 60 kg, there appears to be a higher rate of bleeding with vorapaxar, although an interaction between weight and treatment was not significant.
- Although rare, an increased rate of diplopia and related oculomotor disorders occurred more frequently with vorapaxar treatment compared to placebo (0.2% vs. 0.06%).

TRA 2P Selected Bleeding Endpoints at 3 years^{1,3}

Bleeding Endpoint	Total Study Population				Patients without TIA or stroke history (FDA labeled indication)			
	VORA N=13,225	Placebo N=13,224	HR (95% CI)	P value	VORA N=10,059	Placebo N=10,049	HR (95% CI)	P value

GUSTO moderate or severe	4.2	2.5	1.66 (1.43-1.93)	<0.001	3.7	2.4	1.55 (1.30-1.86)	-
GUSTO severe	-	-	-	-	1.3	1.0	1.24 (0.92-1.66)	-
Intracranial	1.0	0.5	1.94 (1.39-2.70)	<0.001	0.6	0.4	1.46 (0.92-2.31)	-
Fatal	0.3	0.2	1.46 (0.82-2.58)	0.19	0.2	0.2	1.15 (0.56-2.36)	-

CI=confidence interval; GUSTO moderate bleed=requiring transfusion but no hemodynamic compromise; GUSTO severe bleed: intracerebral bleed or resulting in substantial hemodynamic compromise requiring treatment; TIA=transient ischemic attack

Adverse Reactions

Common adverse reactions ¹	Bleeding is the most common adverse reaction with vorapaxar. Other adverse reactions that occurred in 2% or more of the patients and more frequently with vorapaxar than placebo in clinical trials included anemia, depression, rashes, eruptions, and exanthemas.
Death/Serious adverse reactions ¹¹	<u>Deaths:</u> All-cause death for the duration of the TRA2°P study was evaluated as an efficacy endpoint and numerically favored vorapaxar (see Efficacy section). Per the FDA review, all-cause death during treatment + 60 days similarly favored the vorapaxar group (2.6% vs. 2.8%). While cardiovascular deaths were lower, there was an excess in fatal bleeds and fatal strokes as well as a modest excess of non-cardiovascular deaths (mostly due to solid tumors) with vorapaxar compared to placebo. <u>Serious adverse reactions:</u> Per the FDA review, vorapaxar was associated with increased rates of atrial fibrillation, atrial flutter, amyotrophic lateral sclerosis, and upper motor neuron disorder.
Discontinuations due to adverse reactions ¹¹	<u>Due to bleeding:</u> vorapaxar 3% (vs. placebo 1.8%) <u>Due to non-bleeding:</u> vorapaxar 7% (vs. placebo 7.3%)

Drug Interactions

Drug-Drug Interactions¹

- Pharmacokinetic interactions: Vorapaxar undergoes metabolism via the CYP3A4 and CYP2J2 pathways.
 - Avoid use of vorapaxar and strong CYP3A inhibitors due to increased vorapaxar exposure.
 - Avoid use of vorapaxar and strong CYP3A inducers due to decreased vorapaxar exposure.
- Pharmacodynamic interactions: Vorapaxar increases the risk of bleeding.
 - Avoid concomitant use of vorapaxar and warfarin or other anticoagulants. Consider the patient's underlying risk of bleeding before using vorapaxar and other agents that increase bleeding risk.
 - Vorapaxar has only been studied in combination with aspirin and/or clopidogrel and not as a single antiplatelet agent. There is limited experience with vorapaxar and other antiplatelet drugs (e.g., prasugrel, ticagrelor).

Risk Evaluation

As of May 22, 2015

	Comments				
Sentinel event advisories	<ul style="list-style-type: none"> • None • Sources: ISMP, FDA, TJC 				
Look-alike/sound-alike error potentials	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
	Vorapaxar 2.08mg tab	None	None	None	Varivax Voriconazole
	Zontivity	None	None	None	Zorbitive

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations¹

- **FDA review:** The FDA Cardiovascular and Renal Drugs Advisory Committee (RDAC) deliberated on several issues related to the potential FDA approval of vorapaxar (highlights summarized). The inconsistent results in TRA 2P vs. TRACER were explained by the sponsor as related to differences in the patient populations. Evaluation of non-prespecified subgroups (e.g., patients without history of TIA or stroke) for the labeled indication was considered acceptable since the overall trial results were already positive, and the subgroup of patients without stroke or TIA improves safety of vorapaxar. Evaluation of CABG-related bleeding events did not identify a major concern in continuing vorapaxar perioperatively. Management of the finding that patients with low body weight (less than 60 kg) had an unfavorable benefit-risk ratio (no efficacy benefit and increased bleeding) was controversial. Ultimately, language was included in the prescribing information allowing for individual patient and provider consideration rather than a strong warning or contraindication. In considering the overall net benefit risk looking at irreversible, harmful events (e.g., cardiovascular death, MI, stroke, fatal bleed, nonfatal ICH, GUSTO severe bleeding) in the labeled population (no history of stroke or TIA), the sponsor found a positive net benefit-risk.
- **Pharmacokinetics:** Vorapaxar is rapidly absorbed in about an hour after oral administration. Vorapaxar undergoes CYP3A4 and CYP2J2 metabolism and is extensively bound to plasma proteins. The apparent terminal elimination half-life of vorapaxar is 8 days.
- **Pharmacodynamics:** At recommended doses, vorapaxar achieves $\geq 80\%$ inhibition of thrombin receptor agonist peptide (TRAP)-induced platelet aggregation within one week of treatment. Given the long half-life of vorapaxar, 50% of TRAP-induced platelet aggregation inhibition is expected at 4 weeks following discontinuation.
- **Surgery:** With a terminal elimination half-life of 8 days, significant inhibition of platelet aggregation is expected for several weeks following discontinuation of vorapaxar. There are no specific recommendations for management of vorapaxar around surgical procedures provided in the prescribing information. During clinical trials, study investigators were encouraged to continue study drug treatment prior to surgery. In the FDA labeled population (post-MI or PAD patients without TIA or stroke) who underwent CABG surgery, there was a slight excess of major bleeding events and substantially fewer primary endpoint events with vorapaxar compared to placebo.^{1,10}
- **Overdose/Reversal:** There is no known treatment to reverse the effects of vorapaxar. Effects on inhibition of platelet aggregation are expected to last for weeks upon discontinuation of vorapaxar, given its long half-life. Dialysis and platelet transfusions are not expected to provide a benefit.
- **Storage requirements:** Tablets must be stored in original packaging (bottle or blister) until use. Keep bottles tightly closed, and keep the desiccant in the bottle to protect from moisture.

Dosing and Administration¹

- The recommended dose of vorapaxar is 2.08 mg orally once daily, with or without food.
- Vorapaxar was studied as part of combination therapy with aspirin and/or clopidogrel and should be used with aspirin and/or clopidogrel according to their indications or standard of care. There are no data evaluating vorapaxar use as a single antiplatelet agent. There is limited clinical experience with other antiplatelet agents.

Special Populations (Adults)¹

	Comments
Elderly	<ul style="list-style-type: none"> • The median age in TRA2°P was 61 years.³ In the FDA indicated population, one third of patients were 65 years of age and older, and 9% were 75 years or older.¹ No overall differences in safety or effectiveness were observed in older patients compared to younger patients; however, older patients experienced higher rates of bleeding independent of treatment assignment. The increased risk of bleeding

	in older patients should be considered prior to initiating vorapaxar.
Pregnancy	<ul style="list-style-type: none"> • Pregnancy Category B. There are no adequate and well controlled studies of vorapaxar in pregnant women. Based on animal data with studies conducted in rats and rabbits, there is a low probability of an increased risk of adverse developmental outcomes. Animal studies are not always predictive of human response; therefore, vorapaxar should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.
Lactation	<ul style="list-style-type: none"> • It is unknown whether vorapaxar is excreted in human milk, but it is excreted in rat's milk. Because many drugs are excreted in human milk and due to the potential for serious adverse reactions in exposed nursing infants, the manufacturer recommends discontinuing breastfeeding or vorapaxar.
Renal Impairment	<ul style="list-style-type: none"> • No dose adjustment is required in patients with renal impairment.
Hepatic Impairment	<ul style="list-style-type: none"> • No adjustments are needed for patients with mild or moderate hepatic impairment. Vorapaxar is not recommended for use in patients with severe liver impairment due to the inherent increased risk of bleeding in these patients.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified

Projected Place in Therapy

- Dual antiplatelet therapy (DAPT) with aspirin and another agent (e.g., clopidogrel, ticagrelor, prasugrel) is standard of care for patients with a history of ACS as recommended by the American Heart Association/American College of Cardiology (AHA/ACC). Vorapaxar is a novel PAR-1 antagonist antiplatelet agent that was studied as add-on therapy for further reduction in major adverse cardiovascular events in patients with a history of MI, stroke, or PAD.
- When added to standard of care (including antiplatelet therapy with aspirin and/or clopidogrel), vorapaxar was shown to provide a modest benefit in reduction of major cardiovascular events compared to placebo in high risk patients with a history of MI. Vorapaxar was associated with a clinically significant increase in major bleeding events. In considering the addition of vorapaxar, individual factors for increased bleeding risk should be weighed against risk of subsequent cardiovascular events. Of note, in the small PAD subgroup (roughly 14% of the total population), vorapaxar was not associated with a statistically significant improvement in the reduction of major cardiovascular events but was associated with a statistically significant benefit in the reduction of ALI events at the expense of increased bleeding.
- Vorapaxar is contraindicated in patients with a history of stroke, TIA, or ICH. No benefit and increased bleeding was shown when vorapaxar was added to standard therapy in an ACS population. When stratified by weight, the small number of patients weighing less than 60 kg appeared to have a less favorable benefit-risk pattern compared to patients with higher body weight.
- Use of vorapaxar with other anticoagulants should be avoided due to an increased risk of bleeding. Vorapaxar has been studied in combination with aspirin and/or clopidogrel and not as a single agent. There is limited experience with vorapaxar and other antiplatelet agents such as prasugrel and ticagrelor.
- The addition of vorapaxar to the standard of care in the management of patients with prior MI or PAD has not yet been addressed in guidelines from the American Heart Association/American College of Cardiology (AHA/ACC). In the 2015 European Society of Cardiology (ESC) Guidelines for the management of NSTEMI ACS, it is recommended to carefully weigh the modest benefit of the addition of vorapaxar to aspirin and clopidogrel against the increase in bleeding events.¹²
- It is unclear how vorapaxar monotherapy may compare to currently recommended antiplatelet therapies including aspirin monotherapy and clopidogrel monotherapy in the PAD population.^{13,14}

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation Description

High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.