

Brand Name: Zontivity

Generic Name: vorapaxar

Manufacturer: Merck Sharp & Dohme Corp

Drug Class¹⁻⁵: platelet inhibitor

Uses:

Labeled Uses¹⁻⁵:

Myocardial infarction prophylaxis

Stroke prophylaxis

Thrombosis prophylaxis

Mechanism of Action¹⁻⁵:

Reversibly inhibits protease-activated receptor-1 (PAR-1) though its long half-life of 8 days allows it to continuously interact with PAR-1 making it essentially irreversible. Vorapaxar inhibits platelet aggregation induced by thrombin and thrombin receptor agonist peptide (TRAP).

Pharmacokinetics:

Absorption^{1,3}:

T _{max}	1 hour
V _d	424 L
t _{1/2}	~8 days
Clearance	Not reported
Protein binding	>99%
Bioavailability	100% oral

Metabolism^{1,3}: Metabolized primarily by CYP3A4 and CYP2J2 (substrate) and has an active metabolite M20-vorapaxar. It is weak P-glycoprotein inhibitor although based on in vivo trials there are not expected to be any clinically significant glycoprotein interactions.

Elimination^{1,3}: Primarily excretion occurs through feces (58%) as metabolites and 25% is excreted through the urine

Efficacy:

Mahaffey KW, Huang Z, Wallentin L, Storey RF, Jennings LK, Tricoci P, et al. Association of Aspirin dose and Vorapaxar safety and efficacy in patients with non-ST-

segmented elevation acute coronary syndrome (from the TRACER trial). American Journal of Cardiology. 2014. 113(6):936-944.

Study Design: Multicenter, randomized, double-blind, placebo-controlled parallel study

Description of Study: Multiple different sites conducted this study enrolling a total of 12,944 patients with non-ST-segmented elevation acute coronary syndrome. Each patient received either placebo or vorapaxar administered as a loading dose then 2.5 mg/day maintenance dose for at least 1 year. After discharge initially, follow up occurred at 30 days, then at months 4, 8, 12; and every 6 months thereafter. The primary outcome was the incident of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or urgent revascularization. The key secondary outcome was the composite of cardiovascular death, myocardial infarction, or stroke. The study also looked at the average starting dose of aspirin participants were taking before enrollment (low or high dose) and whether the low or high dose aspirin had improved/decreased efficacy with vorapaxar. The primary results showed that vorapaxar was associated with a modest (8%) nonsignificant relative risk reduction in the primary composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or ischemia-driven revascularization. Of the 12,253 patients taking aspirin, ~85% did not change their dose during follow up and few patients changed doses more than once. Adjusted hazard ratios showed trends that in patients treated with higher-dose ASA, vorapaxar was associated with lesser efficacy in reducing cardiovascular outcomes compared with placebo. Vorapaxar was also associated with nominally significant reductions in key secondary outcomes of CV death, MI, or stroke with significant increases in bleeding.

Limitations: The trial was not powered to look specifically at subgroups defined by ASA dosing. The report is considered exploratory. Biases may not have been accounted for or recognized. Also there was funding provided by the manufacturers and also authors were employed by the drug manufacturer.

Conclusion: The study showed that vorapaxar has modest risk reduction when compared to traditional aspirin therapy, there are especially concerns with increased bleeding when combined with new forms of anticoagulation/antiplatelet therapy. Other antiplatelet and anticoagulant therapy has been studied along with vorapaxar and future studies with vorapaxar are needed to determine its efficacy compared to these therapies at optimal dosing regimens.

Morrow, DA, Alberts MJ, Mohr JP, Ameriso SF, Bonaca MP, Goto S, et al. Efficacy and Safety of Vorapaxar in Patients with Prior Ischemic Stroke. Stroke. 2013. 44(3):691-698.

Study Design: multinational, double-blind, randomized, placebo-controlled trial

Description of Study: Patients were enrolled based on prior atherothrombosis (myocardial infarction, peripheral artery disease, or ischemic stroke) then randomly assigned to receive vorapaxar 2.5mg or placebo added to standard antiplatelet therapy. If

the patients had a previous stroke it was in the previous 2 weeks – 12 months. The primary end point was the composite of cardiovascular death, MI, or stroke. In the stroke cohort none of the primary endpoints were reduced with the use of vorapaxar vs placebo. The 3-year incidence of CV death, MI, or stroke was 13.0% in the vorapaxar group compared with 11.7% in the placebo group; hazard ratio (HR) 1.03 (95% confidence interval [CI], 0.85–1.25; P=0.75). There were no other significant differences between the treatment and control group for other end points examined for stroke patients. Combining the cohorts that qualified for the trial with MI or PAD, the risk of intracranial hemorrhage with vorapaxar slightly increased in those with a history of stroke (2.1% vs 0.6%; HR, 2.90; 95% CI, 0.58–14.4; P=0.19) with lower absolute rates among MI or PAD patients without a history of stroke (0.6% vs 0.4%; HR, 1.55; 1.00–2.41; P=0.049; P interaction=0.45). In the 498 patients who qualified for the trial with MI or PAD, who had a history of transient ischemic attack in the absence of a known prior stroke, the risk of intracranial hemorrhage appeared to increase similarly with vorapaxar (1.9% vs 0.5%; HR, 3.86; 95% CI, 0.43–34.5; P=0.23; P interaction versus no TIA, 0.40).

Limitations: The study did not assess if vorapaxar could be effective as an alternative therapy administered alone in comparison with guideline-based antiplatelet therapy.

Conclusion: In this randomized, placebo-controlled, multinational trial, among patients with prior noncardioembolic ischemic stroke, the addition of the protease-activated receptor-1 antagonist vorapaxar to standard therapy did not reduce the rate of major CV events but increased the risk of major bleeding, including intracerebral hemorrhage. These risks need to be weighed before combining these agents to prevent recurrent cardiovascular events.

Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. New England journal of medicine. 2012. 366:1404-1413.

Study Design: multinational, double-blind, placebo-controlled trial

Description of Study: All patients eligible had a history of atherosclerosis (MI or stroke within the last 2 weeks-12 months). Patients were assigned in a 1:1 ratio to receive vorapaxar 2.5mg or placebo. In 2 years 26,449 patients were enrolled in the trial. Of those who qualified 67% had MI, 18% stroke, and 14% peripheral artery disease. 94% of the patients were treated with aspirin upon entering the study. At 3 years cardiovascular death, MI or stroke had occurred in 1028 of the patients (9.3%) in the vorapaxar group compared to 1176 (10.5%) of patients in the placebo group. This gave a hazard ratio of 0.87, (95% CI 0.8-0.94; P<0.001). The rate of CV death or MI was decreased from 8.2% in placebo group to 7.3% in vorapaxar group (P=0.002). Moderate to severe bleeding occurred in 438 patients (4.2%) in the vorapaxar group and 267 patients (2.5%) in the placebo group. (hazard ratio 1.66, 95% CI, 1.43-1.93; P<0.001).

Limitations: The study did not look at previous treatment regimens or adding vorapaxar to initial treatment regimens for the prevention of CV effects. The study was supported by the manufacturer leading to biases.

Conclusion: There was a significant decrease in the rate of CV death, MI, or stroke in patients who had a history of atherothrombosis who were receiving standard therapy, although there was a significant increase in bleeding risk with administration of vorapaxar.

Contraindications^{1,2}: active pathological bleeding (ex. Intracranial hemorrhage or peptic ulcer) and history of stroke, TIA, or intracranial hemorrhage

Precautions^{1,2,3}:

Black box warning: Increased risk of bleeding proportional to underlying bleeding risk (risk factors: low body weight, older age, and reduced renal or hepatic function)

Avoid concomitant use with warfarin or other anticoagulants, strong CYP3A inducers or inhibitors

Adverse Effects^{1,5}:

Occurring in >10% of patients
Bleeding (any grade 25%)

Occurring in <10% of patients
Moderate to fatal bleeding 0.2-3.7%
Anemia 5%
Gastrointestinal hemorrhage 4%
Intracranial hemorrhage 0.4%
Depression 2.4%⁵
Rash 2.2%⁵

Drug Interactions^{1,2}:

Contraindicated: Select strong CYP3A inhibitors (ketoconazole, itraconazole, saquinavir, ritonavir, delavirdine, nelfinavir, lopinavir, tipranavir, posaconazole, boceprevir, telaprevir, cobicistat, atazanavir)

Major interactions:

- Strong CYP3A inhibitors (clarithromycin, nefazodone, indinavir, voriconazole, imatinib, telithromycin, conivaptan), inducers (phenytoin, carbamazepine, primidone, phenobarbital, rifampin, mitotane, rifabutin, fosphenytoin, St. Johns wort, rifapentine, enzalutamine)
- Anticoagulants (heparin, warfarin, phenprocoumon, phenidione, enoxaparin, acenocoumarol, dalteparin, parnaparin, danaparoid, nadroparin, bivalirudin, argatroban, lepirudin, desirudin, fondaparinux, protein C, dapagatran, rivaroxaban, apixaban, reviparin, tinzaparin, ardeparin, certoparin)

Moderate interactions: omega-3 carboxylic acids, omega-3 acid ethyl esters, ticagrelor

Dosing/Administration^{1,5:}

Adult Dosing: 1 tablet (2.08 mg) orally once daily

Geriatrics: 1 tablet (2.08 mg) orally once daily

Renal impairment: no dose adjustment necessary

Hepatic impairment: severe hepatic impairment avoid use, no adjustment in mild-moderate impairment.

Use in special circumstances^{1,5:}

Pregnancy category: B

Lactation: it is unknown if vorapaxar is excreted in breast milk

Conclusion: Vorapaxar can be effectively used to decrease the risk of thrombosis in patients with a history of MI or peripheral artery disease. Patients are at an increased risk for bleeding events and therefore careful patient monitoring and education must be performed to ensure if a bleeding event does occur it will be managed appropriately in a timely manner. The cost of vorapaxar at local pharmacies is about \$280 when using the manufacturer coupon. This price is for a month supply of 2.08mg tablets.⁶ With the study results lacking major efficacy improvement over other antiplatelet therapies and the increased risk of bleeding along with increased cost, the use of this medication will be limited to a narrow range of patients.

Recommended References:

1. Vorapaxar In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
2. Vorapaxar In: Up-To-Date System [Internet database]. Wolters Kluwer Health. Updated periodically.
3. Vorapaxar. Lexi-Drugs [database online]. Lexi-Comp, Inc; August 26, 2014.
4. Vorapaxar package insert. Merck Sharp & Dohme Corp. 2013. Accessed August 26, 2014.
5. Vorapaxar. Clinical Pharmacology [Internet database]. Gold Standard, Inc., 2007. Available at: <http://www.clinicalpharmacology.com>. Accessed: August 26, 2014.
6. Zontivity. GoodRx Inc. 2014. Available at: <http://www.goodrx.com/zontivity>

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