In the United States, heart disease is the number one cause of death, claiming the lives of approximately 600,000 people annually—a staggering 1 in every 4 deaths.\(^1,2\) Coronary heart disease (CHD) alone accounts for nearly 380,000 deaths yearly.\(^3\) Myocardial infarction (MI) is a common type of CHD affecting 720,000 Americans every year. Of these total MIs, 515,000 are first MIs, and 205,000 are recurrent MIs.\(^2\)

Stroke is the fourth leading cause of mortality in the United States, accounting for 1 of every 19 deaths annually.\(^1,3\) In fact, every 4 minutes someone dies of a stroke. Overall, stroke affects an estimated 795,000 Americans annually; of this total, 610,000 are first strokes, and 185,000 are recurrent strokes. In addition, stroke is a leading cause of disability, particularly in individuals aged $\geq 65$ years.\(^3\)

Peripheral arterial disease (PAD), a condition characterized by plaque buildup in the legs, increases the risk for MI and stroke.\(^4\) It is estimated that 1 in every 20 Americans aged $>50$ years has PAD.\(^4\)

CHD accounts for $108.9$ billion total costs annually in the United States.\(^2\) Stroke alone accounts for $38.6$ billion annually in healthcare costs and lost productivity.\(^3\)

Adequate control of hypertension and high low-density lipoprotein cholesterol (LDL-C) has been shown to reduce the risk for stroke and CHD.\(^5,7\) Other factors that may reduce the risk for cardiovascular (CV) disease include exercising, refraining from smoking, and maintaining a healthy diet and weight.\(^1\) Pharmacologic approaches for patients at risk for CV disease include therapies that control hypertension and reduce high LDL-C and/or antithrombotic therapies.\(^8\)

Patients at high risk for thrombotic events may be managed with an antithrombotic drug—either an anticoagulant or an antiplatelet.\(^9\) Many patients who have an MI undergo thrombolysis, a procedure with a clot-dissolving agent, to restore coronary artery blood flow.\(^9\) Other patients may need an urgent coronary revascularization procedure, including a coronary artery bypass graft surgery or a percutaneous intervention to improve blood flow.\(^9\)

For patients with acute coronary syndromes, the use of platelet inhibitors was shown to reduce the rate of thrombotic events; however, these agents are associated with a risk of bleeding.\(^10\) Recently, research has focused on the efficacy and safety of intensifying antiplatelet therapy in patients with established atherosclerosis by adding an agent with a different pharmacologic pathway.\(^11\) One of these pathways targets thrombin, a serine protease that facilitates thrombosis through the selective inhibition of protease-activated receptor (PAR)-1, the main thrombin receptor on human platelets.\(^11\)

### Vorapaxar: A Novel Antiplatelet Treatment Option

On May 8, 2014, the US Food and Drug Administration (FDA) approved vorapaxar (Zontivity; Merck)—the first-in-class PAR-1 antagonist—for the reduction of thrombotic CV events in patients with a history of MI or with PAD.\(^12\) Vorapaxar has been shown to reduce the rate of a combined end point of CV death, MI, stroke, and urgent coronary revascularization.\(^11\)

The FDA approval of vorapaxar was based on the TRA 2P-TIMI 50 (Thrombin Receptor Antagonist in the Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis in Myocardial Infarction) clinical trial, a double-blind, placebo-controlled, phase 3 study that included more than 26,000 patients.\(^11,13\)

The FDA’s labeling requires vorapaxar to be dispensed with a patient medication guide that includes instructions for its use and important safety information. This guide directs healthcare professionals to inform patients about the increased risk for bleeding and bruising associated with this medication and to instruct patients to report any unanticipated, prolonged, or excessive bleeding or blood in the stool or urine.\(^12\)

According to Ellis Unger, MD, Director of the Office of Drug Evaluation in the FDA’s Center for Drug Evaluation and Research, “In patients who have had a heart attack or who have peripheral arterial disease, this drug will lower the risk of heart attack, stroke, and cardiovascular death. In the study that supported the drug’s approval, Zontivity lowered this risk from 9.5 percent to 7.9 percent over a 3-year period—about 0.5 percent per year.”\(^12\)
Dosing and Administration

Vorapaxar is available as a 2.08-mg tablet (equivalent to 2.5 mg of vorapaxar sulfate) and is administered orally once daily, with or without food. The use of vorapaxar with aspirin and/or clopidogrel should follow the indications or standards of care for these medications. There is limited clinical experience with other antiplatelet drugs or with vorapaxar as the only administered antiplatelet agent.13

Mechanism of Action

Vorapaxar reduces the risk for MI and stroke by decreasing the tendency of platelets to form blood clots. Vorapaxar is a reversible antagonist of PAR-1 expressed on platelets, but its long half-life makes it effectively irreversible. In in vitro studies, vorapaxar has been shown to inhibit thrombin-induced and thrombin receptor agonist peptide-induced platelet aggregation.13

The Pivotal TRA 2P-TIMI 50 Clinical Trial

The efficacy of vorapaxar is supported by clinical evidence from the pivotal TRA 2P-TIMI 50 clinical trial, a randomized, double-blind, placebo-controlled phase 3 clinical trial in patients with evidence or a history of atherosclerosis involving the coronary system (ie, spon-

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Table 1

| End points | 3-yr Kaplan-Meier event rate | | | |
| --- | --- | --- | --- | |
| | Placebo, % (N = 13,224) | Vorapaxar, % (N = 13,225) | Hazard ratioa | P value |
| Primary: composite of CV death, MI, stroke, and UCR | 12.4 | 11.2 | 0.88 (95% CI, 0.82-0.95) | .001 |
| Secondary: composite of CV death, MI, and stroke | 10.5 | 9.3 | 0.87 (95% CI, 0.80-0.94) | <.001 |

aVorapaxar group versus placebo group. 
CI indicates confidence interval; CV, cardiovascular; MI, myocardial infarction; UCR, urgent coronary revascularization. 
Source: Zontivity (vorapaxar) tablets prescribing information; May 2014.

Table 2

| Efficacy end points | Placebo (N = 10,090) | Vorapaxar (N = 10,080) | | |
| --- | --- | --- | --- | |
| | Patients with events,a | Kaplan-Meier,b | Patients with events,a | Kaplan-Meier,b | Hazard ratioa | P value |
| Primary: composite of CV death, MI, stroke, UCRa | — | — | 12.4 | 11.2 | 0.88 (95% CI, 0.82-0.95) | .001 |
| Secondary: composite of CV death, MI, strokea | — | — | 10.5 | 9.3 | 0.87 (95% CI, 0.80-0.94) | <.001 |
| Other secondary efficacy end points (first specified event at any time)b | | | | | |
| CV death | 239 (2.4) | 2.8 | 205 (2.0) | 2.4 | 0.86 (95% CI, 0.71-1.03) | NR |
| MI | 569 (5.6) | 6.4 | 470 (4.7) | 5.4 | 0.82 (95% CI, 0.73-0.93) | NR |
| Stroke | 145 (1.4) | 1.6 | 98 (1.0) | 1.2 | 0.67 (95% CI, 0.52-0.87) | NR |
| UCR | 283 (2.8) | 3 | 249 (2.5) | 2.8 | 0.88 (95% CI, 0.74-1.04) | NR |

aEach patient was counted only once in the component of the primary efficacy end point. 
bKaplan-Meier estimate at 1080 days. 
cVorapaxar group versus placebo group. 
dIncluding patients who could have had other nonfatal events or subsequently died. 
CI indicates confidence interval; CV, cardiovascular; MI, myocardial infarction; NR, not reported; PAD, peripheral arterial disease; TIA, transient ischemic attack; UCR, urgent coronary revascularization. 
Source: Zontivity (vorapaxar) tablets prescribing information; May 2014.
taneous MI ≥2 weeks but ≤12 months before the study), the cerebral system (ie, ischemic stroke), or the peripheral vascular system (ie, documented PAD).11,13

The patients were randomized to receive daily treatment with vorapaxar (N = 13,225) or placebo (N = 13,224) in addition to the standard of care. The primary end point was a composite of CV death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization. The secondary end point was a composite of CV death, MI, or stroke. The median follow-up time was 2.5 years (up to 4 years).11,13

Table 1 describes the findings for the primary and secondary efficacy end points.

Table 2 shows the findings in patients with post-MI or PAD and without a history of stroke or transient ischemic attack (TIA). The effect of long-term treatment with vorapaxar on the primary and key secondary end points was maintained for the duration of the trial (median follow-up of 2.5 years, up to 4 years).11,13

Among patients with post-MI or PAD who survived an on-study event, the incidence of subsequent events was lower with vorapaxar. The time from the previous MI to randomization had no relationship to the treatment benefit for the primary study outcome.11,13

Adverse Events

The safety of vorapaxar was evaluated in the TRA 2P-TIMI 50 study, and included 13,186 patients—2187 of whom received treatment with this medication for more than 3 years. The patients randomized to vorapaxar received treatment for a median of 2.3 years.

The most common adverse reactions reported in patients receiving vorapaxar were bleeding, including life-threatening and fatal bleeding.11,13

The results for the bleeding end points in patients with post-MI or PAD and without a history of stroke or TIA are shown in Table 3. Vorapaxar was associated with a 55% increase in moderate or severe bleeding as measured by GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries).11,13

GUSTO severe bleeding was defined as fatal, intracranial, or bleeding with hemodynamic compromise requiring intervention. GUSTO moderate bleeding was defined as bleeding requiring transfusion of whole blood or packed red blood cells without hemodynamic compromise.

Although this study was not designed to evaluate the relative benefits and risks of vorapaxar in individual patient subgroups, patients with a history of stroke, TIA, or

### Table 3 Non–CABG-Related Bleeding Events in Patients with Post-MI or PAD and No History of Stroke or TIA (First Dose to Last Dose + 30 Days) in the TRA 2P-TIMI 50 Study

<table>
<thead>
<tr>
<th>bleeding events</th>
<th>Placebo (N = 10,049)</th>
<th>Kaplan-Meier, %</th>
<th>Vorapaxar (N = 10,059)</th>
<th>Kaplan-Meier, %</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO bleeding categories</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>82 (0.8)</td>
<td>1</td>
<td>100 (1.0)</td>
<td>1.3</td>
<td>1.24 (95% CI, 0.92-1.66)</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>199 (2.0)</td>
<td>2.4</td>
<td>303 (3.0)</td>
<td>3.7</td>
<td>1.55 (95% CI, 1.30-1.86)</td>
</tr>
<tr>
<td>Any GUSTO bleeding (severe, moderate, mild)</td>
<td>1769 (17.6)</td>
<td>19.8</td>
<td>2518 (25.0)</td>
<td>27.7</td>
<td>1.52 (95% CI, 1.43-1.61)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>14 (0.1)</td>
<td>0.2</td>
<td>16 (0.2)</td>
<td>0.2</td>
<td>1.15 (95% CI, 0.56-2.36)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>31 (0.3)</td>
<td>0.4</td>
<td>45 (0.4)</td>
<td>0.6</td>
<td>1.46 (95% CI, 0.92-2.31)</td>
</tr>
<tr>
<td>Clinically significant bleedingb</td>
<td>950 (9.5)</td>
<td>10.9</td>
<td>1349 (13.4)</td>
<td>15.5</td>
<td>1.47 (95% CI, 1.35-1.60)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>297 (3.0)</td>
<td>3.5</td>
<td>400 (4.0)</td>
<td>4.7</td>
<td>1.37 (95% CI, 1.18-1.59)</td>
</tr>
</tbody>
</table>

*Kaplan-Meier estimate at 1080 days.

*bClinically significant bleeding includes any bleeding requiring medical attention, including intracranial hemorrhage, or clinically significant overt signs of hemorrhage associated with a drop in hemoglobin (Hb) of ≥3 g/dL (or, when Hb is not available, an absolute drop in hematocrit of ≥15% or a fall in hematocrit of 9 to <15%).

+CABG indicates coronary artery bypass graft surgery; CI, confidence interval; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; MI, myocardial infarction; PAD, peripheral arterial disease; TIA, transient ischemic attack.

Source: Zontivity (vorapaxar) tablets prescribing information; May 2014.
intracranial hemorrhage (ICH) showed an increased risk for ICH events.\textsuperscript{11,13}

**Contraindications**

The use of vorapaxar is contraindicated in patients with a history of stroke, TIA, or ICH, because of an increased risk for ICH in this patient population. Vorapaxar is also contraindicated in patients with pathologic bleeding, such as ICH or peptic ulcer.\textsuperscript{13}

**Warnings and Precautions**

**Boxed warning.** The prescribing information for vorapaxar includes a boxed warning about the risk for bleeding. Vorapaxar should not be used in patients with a history of stroke, TIA, ICH, or active pathologic bleeding. Furthermore, antiplatelet agents, including vorapaxar, increase the risk for bleeding, including ICH and fatal bleeding. Vorapaxar increases a patient’s risk for bleeding in proportion to the patient’s underlying bleeding risk. Before initiating vorapaxar therapy, the underlying risk for bleeding should be considered.\textsuperscript{13}

**General risk for bleeding.** Antiplatelet agents, including vorapaxar, increase the risk for bleeding, including ICH and fatal bleeding. Vorapaxar increases a patient’s risk for bleeding in proportion to the patient’s underlying bleeding risk. Before initiating vorapaxar therapy, the underlying risk for bleeding should be considered.\textsuperscript{13}

**Strong cytochrome P3A inhibitors or inducers.** Vorapaxar is eliminated primarily by metabolism, with contributions from cytochrome (CYP) P3A4 and CYP2J2. Strong CYP3A inhibitors increase vorapaxar exposure. Vorapaxar should not be used with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, neflunavir, indinavir, boceprevir, telaprevir, telithromycin, and conivaptan). Strong CYP3A inducers decrease vorapaxar exposure. Vorapaxar should not be used with strong inducers of CYP3A (e.g., rifampin, carbamazepine, St. John’s Wort, and phenytoin).\textsuperscript{13}

**Use in Specific Populations**

**Pregnancy.** There are no adequate and well-controlled studies of vorapaxar use in pregnant women. Vorapaxar should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus.\textsuperscript{13}

**Nursing mothers.** Nursing should be discontinued in patients receiving vorapaxar, or vorapaxar should be discontinued in a nursing mother.\textsuperscript{13}

**Renal impairment.** No dose adjustment is needed in patients with renal impairment.\textsuperscript{15}

**Hepatic impairment.** In patients with mild and moderate hepatic impairment, no dose adjustment is required. Based on the increased risk for bleeding in patients with severe hepatic impairment, vorapaxar is not recommended in these patients.\textsuperscript{13}

**Overdose.** There is no known treatment to reverse the antiplatelet effect of vorapaxar; if bleeding occurs after a vorapaxar overdose, neither dialysis nor platelet transfusion can be expected to be beneficial. The inhibition of platelet aggregation can be expected for weeks after the discontinuation of normal dosing. There is no standard test available to assess the risk for bleeding in an overdose situation.\textsuperscript{13}

**Conclusion**

Vorapaxar, the first-in-class PAR-1 antagonist to receive FDA approval, represents a new antiplatelet treatment option for patients at high risk for MI, stroke, or CV death, namely, patients with a history of MI or with PAD. In a clinical trial involving more than 26,000 patients, treatment with vorapaxar, in addition to the standard of care, was shown to reduce the rate of a composite end point of CV death, MI, stroke, and the need for urgent coronary revascularization procedures.

The most common adverse reaction reported in patients receiving vorapaxar is bleeding, including life-threatening and fatal bleeding.

**References**