Prasugrel (Effient), an Adenosine Diphosphate Receptor Antagonist for the Treatment Of Acute Coronary Syndrome

Miren E. Jauregui, PharmD, Ogochukwu U. Umejei, PharmD, and Martin P. Cruz, PharmD, CGP, BCPP

INTRODUCTION

The acute coronary syndrome (ACS) includes heart attacks and unstable angina (UA). Coronary heart disease, which can result in ACS, affects nearly 1.5 million people in the U.S. annually.¹ When the arteries become narrowed and clogged by cholesterol and fat deposits, cardiac arrest is a major manifestation of coronary heart disease. In some cases, the plaque can rupture, resulting in a blood clot. Blood clots can then partially or completely block the supply of blood to the heart, resulting in ACS.²

There are several subtypes of ACS, including unstable angina and two forms of myocardial infarction (MI) based on their appearance (Figure 1).³,⁴ Most patients with ACS undergo percutaneous coronary intervention (PCI), which usually includes placement of a stent to re-open the clogged artery. Initial therapy includes reperfusion, antiplatelet drugs, antithrombin, nitrates, morphine, and beta blockers as well as other measures.

During an ACS episode, adhesion, activation, and aggregation of the platelets are stimulated. When the plaque ruptures, it exposes collagen and von Willebrand factor, to which circulating platelets adhere. Following adhesion, multiple metabolic pathways are stimulated within the platelet, resulting in the production and release of thromboxane A₂ (TXA₂), adenosine diphosphate (ADP), and other substances from platelet granules. These products stimulate more platelet recruitment, activation, and vasoconstriction and lead to platelet aggregation by activating the glycoprotein IIb/IIIa (GP IIb/IIIa) complex, which binds platelets to one another.⁵,⁶

CHEMISTRY AND PHARMACOLOGY

Prasugrel (Effient, Daiichi Sankyo/Lilly), was first approved in Europe as Efient. It belongs to the thienopyridine class of antiplatelet drugs such as ticlopidine (Ticlid, Roche) and clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Aventis). It exerts its effects by irreversibly blocking the platelet receptor P2Y₁₂, ADP, thus inhibiting platelet function. Because prasugrel is a prodrug, it must be converted to its pharmacologically active form in order for it to exert effects in the body. The conversion of prasugrel to its active component takes place via rapid hydrolysis by esterases, followed by a single cytochrome P450 (CYP)–dependent step. The drug’s active metabolite contains a thiol group that binds to a free cysteine on the P2Y₁₂ receptor. It is through this mechanism that ADP binding and activation are irreversibly blocked.⁶

Prasugrel reduces the tendency of platelets to stick or clump together by blocking the P2Y₁₂, ADP receptor on the platelet’s surface. Clumping of platelets can cause clogged arteries and may lead to a heart attack.

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Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Electrocardiogram</th>
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<tbody>
<tr>
<td>ST-elevation</td>
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<tr>
<td>No ST-elevation</td>
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</tbody>
</table>

Cardiac markers

<table>
<thead>
<tr>
<th>positive</th>
<th>negative</th>
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<tbody>
<tr>
<td>Unstable angina</td>
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Myocardial Infarction

<table>
<thead>
<tr>
<th>Q-wave MI</th>
<th>non–Q-wave MI</th>
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<tbody>
<tr>
<td>STEMI</td>
<td>NSTEMI</td>
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Figure 1  Classification of acute coronary syndrome. MI = myocardial infarction; STEMI = ST-segment elevation MI; NSTEMI = non–ST-segment elevation MI; ST = ST-segment elevation of electrocardiographic tracing. (Adapted from Grech ED, Ramsdale DR. BMJ 2003;326[7401]:1259–1261;³ and Alpert JS, et al. J Am Coll Cardiol 2000;36[3]:959–969.⁴)
The drug’s formula is C_{20}H_{20}FNO_{3}S.

**PHARMACOKINETICS AND PHARMACODYNAMICS**

Prasugrel inhibits platelet aggregation within 15 to 30 minutes and usually peaks at about two hours. The drug is rapidly absorbed orally and is extensively metabolized by the liver. About 70% of the drug is excreted through the kidneys, and 27% is eliminated via the feces. The active metabolite (R-138727) has a half-life of approximately eight hours. In vitro studies indicate that active metabolite generation occurs primarily by CYP 3A and CYP 2B6; R-95913 and R-138727 would not be expected to significantly inhibit CYP 1A2, 2C9, 2C19, 2D6, or 3A-mediated in vivo metabolism of coadministered drugs.

Table 1 shows the pertinent pharmacokinetic and pharmacodynamic data for prasugrel.

**CLINICAL TRIALS**

The TRITON–TIMI 38 Trial

TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction), which enrolled 13,608 patients with ACS, compared prasugrel with clopidogrel, both in combination with aspirin. As a more potent antiplatelet agent, prasugrel reduced the combined rate of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (12.1% mortality for clopidogrel and 9.9% for prasugrel).

In TRITON, when prasugrel was taken with aspirin, it reduced the relative risk of the combined endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke by 19% more than when clopidogrel was taken with aspirin. These benefits were accompanied by an increased risk of serious bleeding with prasugrel overall, a risk that included life-threatening and even fatal bleeding.

When the risk of this type of bleeding was compared with the benefit of reduced heart attack, there were five more TIMI major bleeding events but 22 fewer heart attacks for every 1,000 patients treated with prasugrel compared with every 1,000 patients treated with clopidogrel. The difference in overall risk of cardiovascular death and the risk of increased stroke was not significant between treatment groups.

The JUMBO–TIMI 26 Trial

JUMBO–TIMI 26 (Joint Utilization of Medications to Block Platelets Optimally–TIMI) was the first phase 2 study of a dose-ranging safety trial comparing the primary endpoint of clinically significant bleeding (TIMI minor or major) in patients receiving prasugrel or clopidogrel. A total of 904 patients undergoing PCI received 325 mg of enteric-coated aspirin and were randomly assigned to receive a loading dose of clopidogrel 300 mg and a maintenance dose of 75 mg, or prasugrel in combinations of 40 mg/7.5 mg, 60 mg/10 mg, or 60 mg/15 mg. At 30 days, bleeding rates were 2.4% with clopidogrel 300 mg/75 mg, 1.5% with prasugrel 40 mg/7.5 mg, 2% with prasugrel 60 mg/10 mg, and 1.6% with prasugrel 60 mg/15 mg. The study revealed a nonsignificant reduction in major adverse cardiovascular events after evaluation of secondary efficacy endpoints.

**DRUG–DRUG INTERACTIONS**

Coadministration of prasugrel and warfarin increases the risk of bleeding. Taken with chronic nonsteroidal anti-inflammatory drugs (NSAIDs), it may increase the risk of bleeding. Prasugrel can be given with inducers or inhibitors of CYP 450 enzymes, and it can be taken

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Table 1 Pharmacokinetic and Pharmacodynamic Parameters of Prasugrel

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prasugrel</th>
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<tbody>
<tr>
<td>Bioavailability</td>
<td>Unknown; may be decreased by increased gastric pH</td>
</tr>
<tr>
<td>Protein binding</td>
<td>5%–15%</td>
</tr>
<tr>
<td>Onset of action</td>
<td>30 minutes to 4 hours for maximal effect (following a 60-mg loading dose)</td>
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<tr>
<td>Platelet aggregation inhibition (assessed by various methods)</td>
<td>78.8% ± 9.2% (single doses of 60 mg)</td>
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<tr>
<td></td>
<td>60% (multiple daily doses of 10 mg)</td>
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<tr>
<td>Duration of effect</td>
<td>More than 3 days</td>
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<tr>
<td>Metabolism</td>
<td>Active metabolite formation via CYP 3A4 and CYP 2B6 (and CYP 2C9 and 2C19 to a lesser extent); weak inhibitor of CYP 2B6</td>
</tr>
<tr>
<td>Elimination</td>
<td>68%–70% via urine; 27% via feces</td>
</tr>
<tr>
<td>Adverse drug events</td>
<td>Renal bleeding, thrombocytopenia (0.3%), neutropenia (&lt;0.1%), colonic neoplasms (0.2%); data not available for other adverse events</td>
</tr>
</tbody>
</table>


CYP = cytochrome P450; GI = gastrointestinal.
with aspirin (75–325 mg/day), heparin, GPIIb/IIIa inhibitors, statins, digoxin, and drugs that raise gastric pH, including proton pump inhibitors and H₂ blockers.

**DOSEAGE AND ADMINISTRATION**

Treatment with prasugrel is initiated with a single 60-mg oral loading dose after cardiac catheterization, followed by a maintenance dose of 10 mg orally once daily, with or without food. For patients weighing less than 60 kg, 5 mg once daily can be considered. Patients should also take aspirin (75–325 mg) daily.1,14

**WARNINGS AND PRECAUTIONS**

Pecutions should be taken in patients with a history of bleeding disorders.3,12

A boxed warning states that prasugrel can cause significant, sometimes fatal, bleeding. This agent should not be used in patients with active pathological bleeding or a history of transient ischemic attack or stroke. In patients 75 years of age or older, prasugrel was not generally recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (with diabetes or a prior MI), where its effect appears to be greater.13

Prasugrel should not be initiated in those patients likely to undergo urgent coronary artery bypass graft surgery. When possible, the drug should be discontinued for at least seven days before any surgery.15

If possible, bleeding should be managed without discontinuing prasugrel. Stopping the drug, particularly in the first few weeks after an ACS, increases the risk of a subsequent cardiovascular event.13

**ADVERSE REACTIONS**

Indigestion is the most commonly reported gastrointestinal side effect associated with prasugrel.15 in TRITON–TIMI 38, more cases of colonic neoplasm were observed with prasugrel (13 events in 6,813 patients) than with clopidogrel (four events in 6,795 patients) (P = 0.03).14

The incidence of TIMI major bleeding was higher with prasugrel than with clopidogrel in TRITON–TIMI 38 (2.4% vs. 1.8%; hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.03–1.68; P = 0.03). At the end of the study, rates of life-threatening bleeding were also higher in the prasugrel group than in the clopidogrel group (1.4% vs. 0.9%; HR, 1.52; 95% CI, 1.08–2.13; P = 0.01).14 However, the prasugrel patients had a net clinical benefit in comparison with clopidogrel patients (HR, 0.87; 95% CI, 0.79–0.95; P = 0.004) based on efficacy and safety endpoints, which included death.14

Other adverse effects observed with prasugrel during clinical trials included dizziness, headache, epistaxis, hema toma, and bruising.5,7,12–15

**MONITORING REQUIREMENTS**

No specific serum drug level is required in monitoring patients receiving prasugrel. Complete blood counts with differential, bleeding time, and liver function tests should be routinely monitored during prasugrel therapy.

**CONCLUSION**

Patients with ACS who undergo an artery-opening procedure now have a new treatment option to help prevent heart attacks in the future. In February 2009, the European Commission approved prasugrel (Efient) for the prevention of atherothrombotic events in patients with ACS undergoing PCI. The FDA approved prasugrel in July 2009 for patients in the U.S.

Before the approval, the FDA had extended its review by an additional three months from the original designated priority of six months. Three problems appeared to have impeded the FDA’s decision: an increase in minor and major bleeding and concerns of related deaths in the prasugrel arm; the discovery of more cancers in the prasugrel group compared with the clopidogrel group in TRITON; and a formulation issue related either to the active ingredient or to the excipient substance.

On the basis of the clinical trials, prasugrel appears to be a promising option in patients at high risk for ischemic events, including diabetic patients and individuals who cannot tolerate clopidogrel plus aspirin therapy.

**REFERENCES**


2. Heart disease guide: Coronary artery disease. WebMD/Cleveland Clinic. Available at: www.webmd.com/heart-disease/guide/heart-disease-coronary-artery-


