FDA Advisory Committee Meeting on Prasugrel For Acute Coronary Syndromes

Walter Alexander

On February 3, 2009, the FDA's Cardiovascular and Renal Drugs Advisory Committee voted affirmatively on a New Drug Application for prasugrel HCl 5 and 10 mg (proposed name, Effient). At a meeting in Silver Spring, Maryland, the panel voted unanimously (9–0) to approve the drug for the treatment of acute coronary syndromes (ACS) in patients with either unstable angina/non–ST-segment elevation myocardial infarction (UA/NSTEMI) or STEMI. The FDA is not constrained to follow the panel's recommendations, but it usually does. If approved, prasugrel would be the first within its class to compete with clopidogrel (Plavix), which is scheduled to go off-patent in 2011 in the U.S.

- J. Anthony Ware, MD, Vice-President, Lilly Research Laboratories, Indianapolis, Ind.

Prasugrel, which was approved in Europe on February 23, is considered the most important drug in Eli Lilly's pipeline. Presenting for the drug's sponsors (Daiichi Sankyo, Inc., and Lilly), Dr. Ware noted that the proposed indications were for (1) unstable angina (UA) or NSTEMI managed with percutaneous coronary intervention (PCI) and (2) STEMI managed with primary or delayed PCI.

He explained that prasugrel has been shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke and to prevent stent thrombosis. The new thienopyridine's faster, higher, and more consistent inhibition of platelet function, as compared with clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Aventis), is expected to produce important clinical benefits for patients with ACS.

- Eugene Braunwald, MD, Distinguished Hersey Professor of Medicine, Harvard Medical School, and Chairman, TIMI Study Group, Brigham and Women's Hospital, Boston, Mass.
- Jeffrey S. Riesmeyer, MD, Senior Clinical Research Physician, Prasugrel Product Team Medical Fellow, Eli Lilly, Indianapolis, Ind.
- Elliott Antman, MD, Professor of Medicine, Harvard Medical School, and Director, Samuel A. Levine Cardiac Unit, Brigham and Women's Hospital, Boston, Mass.

Dr. Braunwald, who was listed as an external consultant, said that there are 1.57 million hospital admissions for ACS annually in the U.S., indicating a significant unmet medical need. He noted the limitations of clopidogrel, the current standard, pointing to its modest antiplatelet effect, high variability in responses among patients, and delayed onset of action. He underscored that evidence from clinical trials strongly suggests that the lesser clopidogrel response leads to increased risks of MI and stent thrombosis.

Discussing prasugrel's pharmacology, Dr. Riesmeyer said that the benefits of prasugrel, relative to clopidogrel, can be attributed to more effective platelet inhibition from the higher active metabolite concentrations achieved through prasugrel's loading dose and higher response rates with prasugrel's 10-mg maintenance dose.

Dr. Antman gave the core of the sponsors' presentation—the results of TRITON-TIMI 38 (Trials to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction). This study was a 12-month double-blind comparison of clopidogrel (with a 300-mg loading dose and a 75-mg maintenance dose) and prasugrel (with a 60-mg loading dose and a 10-mg maintenance dose). All patients received aspirin. TRITON-TIMI 38 included 13,600 ACS patients with planned PCI.

The findings show a balance of efficacy and safety, Dr. Antman said, with CV death, MI, and stroke rates (the combined primary endpoint) of 12% at 450 days for clopidogrel and 9.9% for prasugrel ($P = 0.0004$). The number needed to treat for that benefit was 46.

The rate of TIMI Major Bleeding after non–coronary artery bypass grafting (CABG), however, was higher for prasugrel at 2.4%, compared with a rate of 1.8% for clopidogrel ($P = 0.03$). The number needed to harm was 167.

TIMI Major Bleeding was defined as any intracranial hemorrhage or overt bleeding requiring intervention associated with a decrease in hemoglobin of 5 g/dL or more. Both the UA/NSTEMI and STEMI patients experienced significant benefits with prasugrel (UA/NSTEMI, $P = 0.002$; STEMI, $P = 0.019$). Benefits were found consistently as well at 30, 60 and 90 days.

In a prospectively defined landmark analysis, the primary endpoint also favored the prasugrel loading dose significantly at three days (4.7% vs. 5.6% for clopidogrel; $P = 0.01$) and the maintenance dose at 450 days (5.6% vs. 6.9% for clopidogrel; $P = 0.003$).

Although an assessment of net clinical benefit (death, MI, stroke, and TIMI Major Bleeding) favored prasugrel (12.2% vs. 13.9% for clopidogrel; $P = 0.004$), a *post hoc* evaluation found that the advantage disappeared in patients 75 years of age and older. Clopidogrel was slightly favored in patients weighing less

than 60 kg (132 pounds).

After three days, the rates of non-CABG TIMI Major Bleeding were 4.82% for prasugrel in patients 75 years of age and older and 3.62% for those younger than age 75. The sponsors' recommendation, therefore, was to reduce the prasugrel maintenance dose for patients weighing less than 60 kg and for patients 75 years of age and older. The potential mitigation of bleeding risk may also be achieved by choosing a radial instead of a femoral catheter access during PCI, with prasugrel contraindicated for patients who have had a prior transient ischemic attack (TIA) or stroke.

Summing up the public health implications, Dr. Braunwald said that prasugrel had the potential to prevent 23,000 MIs; 8,600 urgent target-vessel revascularizations; 7,400 stent thromboses; and 4,000 deaths—at a cost of 2,300 cases of nonfatal major bleeding (in non-CABG patients).

- Ellis F. Unger, MD, Team Leader, General Medicine Branch, FDA Cardiovascular and Renal Drugs Advisory Committee, Center for Biologics Evaluation and Research

Largely concurring with the sponsors' main findings, Dr. Unger noted that patient management in TRITON-TIMI 38 was consistent with contemporary practice and that benefits were persuasive across UA/NSTEMI patients, STEMI patients, and the overall ACS populations. Results were driven by nonfatal MI with positive trends on mortality rates. Stroke findings were neutral. In addition, prasugrel's superiority generally occurred early in treatment. For STEMI in particular, benefits were experienced immediately, with curves parallel thereafter. Overall, 54% of adverse events (AEs) occurred in the first week, with 45% in the first day.

Dr. Unger further noted that positive results were consistent for all demographic subgroups with concomitant diseases, for all stent types, and with the use of glycoprotein (GPIIb/IIIa) inhibitors. Rates of AEs were higher for prasugrel, however, in patients with a history of stroke (19.1% vs. 14.1% for clopidogrel).

Bleeding also occurred early during therapy; one-third of AEs were reported on the first day, and nearly half were reported within the initial seven days. In an analysis of TIMI Major or Minor Bleeding (clinically overt bleeding associated with a decrease in hemoglobin of between 3 and 5 g/dL), Dr. Unger emphasized that the relative risk of bleeding with prasugrel was not particularly high in patients who were younger than 70 years of age (1.31%) or in those 70 years of age and older (1.35%). At the same time, however, bleeding was malignant, resulting in fatal hemorrhage in nine of 891 patients receiving prasugrel (1% of patients), compared with one of 894 patients receiving clopidogrel (0.1% of patients). Symptomatic intracranial hemorrhage was reported in 0.8% of prasugrel patients in this subgroup and in 0.3% of patients in the clopidogrel group.

Dr. Unger discussed TRITON's findings of an increased number of new cancers and worsening of existing cancers that could be consistent with tumor stimulation. Citing a lack of a purported mechanism and inconclusive data about neoplasms, he said that the agency's review indicated that prasugrel did not cause cancer. The sponsors' report had suggested that ascertainment bias was responsible for the apparent increase when bleeding led to the discovery of colorectal cancers that otherwise would not have been detected.

- Douglas Weaver, MD, Professor of Medicine, Wayne State University, and Division Head of Cardiovascular Medicine, Darin Chair of Cardiology, Director, Henry Ford Cardiovascular Institute, Henry Ford Health System, Detroit, Mich.
- Victor L. Serebruany, MD, PhD, Johns Hopkins University Medical School, Baltimore, Maryland
- Thomas Marciniak, MD, Medical Team Leader, FDA Cardiovascular and Renal Unit

Representing the American College of Cardiology, Dr. Weaver delivered one of two statements offered in the open public hearing portion of the meeting. He called for a postmarketing registry, beyond the usual manufacturer's postmarketing surveillance, to monitor safety and to ensure the safety profile of this "new but important drug."

The second statement, by well-known platelet researcher Dr. Serebruany, who is also a prasugrel patent application holder with Lilly, reflected less certainty about the drug's efficacy and some uncertainty about its safety. In a follow-up interview, he expressed dismay that the primary data, now available from the full 357-page FDA report, had not been made public until a few days before the hearing. He further said that cancer rates were much higher and broader than reported. He also dismissed the claim that cancer increases were caused by ascertainment bias.

Dr. Serebruany explained that the dramatically more powerful chronic antiplatelet effects of prasugrel could allow pre-existing cancer cell colonies to break through the weakened platelet barrier and facilitate metastatic dissemination. The fact that the difference in cancers becomes apparent at four months after randomization in TRITON clearly supports this hypothesis. His main complaint, however, was over the definition of MI in the primary endpoint, which was changed to include transient increases in biomarkers. If the analysis had considered only those MIs reported by clinicians during PCI, the benefit in the UA/NSTEMI arm, the STEMI cohort, and the overall TRITON population would have disappeared after the first three days. The FDA report clearly acknowledges that the outcome curves are identical and parallel for the rest of the 14.5 months of follow-up.

Dr. Marciniak, in the Prasugrel Secondary Review, concluded that the efficacy results showed a small (on the order of one event for every 100 patients), early benefit (in less than 30 days) that was related to a reduction in MIs.

He said, "Whether the benefit increases beyond 30 days is less clear, but it is very clear that significant bleeding increases continuously with time, and the potential for tumor promotion remains a serious question for long-term use."

Finally, Dr. Serebruany noted that two oral agents currently in development, Schering's TRA-SCH 530348 (in phase 3) and Eisai's E555 (in phase 2), both thrombin receptor antagonists, might be effective with less bleeding risk than prasugrel and clopidogrel because they target the thrombin receptor and "only very slightly" affect adenosine diphosphate and collagen receptors. ■