FDA Panel Backs Approval of Ticagrelor for ACS

BY ALICIA AULT

FROM A MEETING OF THE FDA'S CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

COLLEGE PARK, MD. — The Food and Drug Administration's Cardiovascular and Renal Drugs Advisory Committee voted 7-1 to recommend approval of the platelet inhibitor ticagrelor to treat non–ST elevation myocardial infarction and ST-elevation myocardial infarction in patients intended to receive primary coronary intervention or who would be managed medically.

The panel did not directly address other indications being sought by ticagrelor's maker, AstraZeneca, including in unstable angina and after a coronary artery bypass graft (CABG). But in an interview after the meeting, FDA official Robert Temple said that the panel had basically covered all the populations that would be considered under the rubric of acute coronary syndrome. As the agency weighs approval, it will decide whether to grant specific indications, said Dr. Temple, who is head of the office reviewing ticagrelor (Brilinta).

The committee chair urged the FDA to require a postapproval study that would include a substantial number of Americans and look in particular at unstable angina.

According to the company, ticagrelor is the first reversibly binding oral adenosine diphosphate receptor antagonist. It selectively inhibits P2Y12, a key target receptor for ADP.

FDA committee member Mori J. Krantz was the lone panelist who voted against approval. He said that he was concerned about data from the pivotal PLATO (A Study of Platelet Inhibition and Patient Outcomes) study showing that patients in the United States did not fare as well as those in overseas sites.

"That it went in the opposite direction is a little discomforting," said Dr. Krantz of the University of Colorado, Denver.

Committee chairman Sanjay Kaul voted in favor of approval, but said, "I am concerned, however, about the data going in the wrong direction in the United States." He urged the FDA to require a postapproval study that would include a substantial number of Americans and look in particular at unstable angina.

The FDA generally follows its panels' advice.

The PLATO data was first presented at the European Society of Cardiology in 2009 and published online in the New England Journal of Medicine in August 2009. The randomized, double-blind trial compared ticagrelor to clopidogrel in all-comer ACS patients. The study enrolled 18,624 patients at 862 centers in 43 countries.

AstraZeneca said that PLATO proved that ticagrelor was superior to clopidogrel, with a 16% reduction in relative risk for the primary composite end point of cardiovascular death, myocardial infarction, or stroke. The company claimed there was no difference in major bleeding as defined by the trial, but acknowledged that there was a slightly higher number of patients with intracranial hemorrhage, including fatal hemorrhage.

The FDA reviewers said they also found a higher rate of bleeding after CABG.

But the main concern—and the primary reason for the panel meeting—was why there were more cardiovascular events in Americans. AstraZeneca said that a post hoc analysis determined that Americans were taking higher doses of aspirin, which led to more heart attacks, strokes, and deaths.

After lengthy debate, the committee said the difference could not be attributed to chance alone or to the aspirin dosages. Differences in clinical practice in the United States were the more likely explanation, said a number of panelists.

Members of FDA advisory panels have been cleared of conflicts related to the topic under discussion. The agency is due to make a decision on the application for approval by Sept. 18. ■