Summary Minutes of the
Cardiovascular and Renal Drugs Advisory Committee
February 3, 2009

Location: Hilton Washington DC/Silver Spring, Maryland Ballroom,
8727 Colesville Road, Silver Spring, MD.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

These summary minutes for the February 3, 2009 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on February 24, 2009.

I certify that I attended the February 3, 2009 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

----------/s/----------
Elaine Ferguson M.S.,R.Ph.
Designated Federal Official

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Marvin Konstam, M.D.
Acting Committee Chair

Meeting of the Cardiovascular and Renal Drugs Advisory Committee

February 3, 2009

The Cardiovascular and Renal Drugs Advisory Committee, Center for Drug Evaluation and Research met on February 3, 2009 at the Hilton Washington DC/Silver Spring, Maryland Ballroom, 8727 Colesville Road, Silver Spring, MD. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. There were approximately two hundred persons in attendance.

Issue: The committee discussed new drug application (NDA) 22-307, prasugrel hydrochloride film coated oral tablets, 5 milligrams (mg) and 10 mg, Eli Lilly and Company, for the proposed indication for use in acute coronary syndrome.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):

Steven D. Findlay M.P.H.(Consumer Representative), John M. Flack M.D., M.P.H., Mori Krantz, M.D., F.A.C.C., James D. Neaton, Ph.D., Emil P. Paganini, M.D., F.A.C.P., F.R.C.P.

Special Government Employee Consultants (Voting):

Marvin A. Konstam, M.D. (Acting Chair), Richard Cannon, M.D., Michael Domanski, M.D., James E. Udelson, M.D.

Industry Representative Members Present (Non-Voting):

Jonathan C Fox, MD, PhD, FACC

FDA Participants (Non-Voting):

John Jenkins, M.D., Robert Temple, M.D., Norman Stockbridge, M.D.

Open Public Hearing Speakers: W. Douglas Weaver M.D., American College of Cardiology, Victor Serebruany M..D.;

Acting Designated Federal Official:

Elaine Ferguson M.S., R.Ph.

The agenda was as follows:

8:00 a.m.	Call to Order Introduction of Committee	Marvin A. Konstam, M.D Acting Chair
	Conflict of Interest Statement	Elaine Ferguson, M.S.,R.Ph. Designated Federal Official, CRDAC
8:05 a.m.	FDA Opening Remarks	Norman Stockbridge, M.D. Director, Cardiovascular and Renal Drug Products, CDER
8:15 a.m.	Sponsor Presentations	
	Introduction	J. Anthony Ware, MD Vice President, Lilly Research Laboratories Diabetes, Cardiovascular, and Acute Care Platform
	Unmet Medical Need	Eugene Braunwald, M.D. Hersey Distinguished Professor of Theory and Practice of Medicine, Harvard Medical School Chairman, TIMI Study Group, Brigham and Women's Hospital
	Dosing Considerations	Jeffrey Riesmeyer, M.D. Medical Fellow, Cardiovascular Medicine Eli Lilly and Company
	Benefit-Risk (TRITON-TIMI 38)	Elliott M. Antman, M.D. Professor of Medicine, Harvard Medical School Senior Investigator, TIMI Director of Samuel A. Levine Cardiac Unit, Brigham and Women's Hospitals
	Special Topics	William Macias, M.D., Ph.D. Senior Medical Director, Cardiovascular Acute Care Eli Lilly and Company
	Closing Remarks	Eugene Braunwald, M.D.
9:45 a.m.	Questions to presenters	
10:15 a.m.	Break	
10:30 a.m.	FDA Presentation	Ellis F. Unger, M.D. Deputy Director Division of Cardiovascular and Renal Products Office of Drug Evaluation-I Office of New Drugs CDER, FDA
11:30 a.m.	Questions to presenters	
12:00	Lunch	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	Discussion of questions to committee	
3:30 p.m.	Break	
3:45 p.m.	Discussion of questions to committee (continued)	
5:00 p.m.	Adjourn	

Questions to the Committee

1.1 Was the primary end point meaningful? In particular, comment on the strategy for assessing MI. Ordinarily, the investigator-reported events and the adjudicated events differed little, but, in TRITON, only about half of the events were identified by investigators. Is there a concern that the additional events, generally asymptomatic peri-procedural MIs, lack clinical significance? What are the long-term consequences of non-fatal myocardial infarction?

Consensus… Yes, the primary end point was meaningful and there is evidence indicating that tissue damage indicated by enzyme elevation has long term consequences. l.

1.2 Clopidogrel has established benefits on these events compared with placebo. Based on the results of TRITON, can we infer that prasugrel would also be superior to placebo?

Consensus… Yes

1.3 Prasugrel was superior to clopidogrel in both UA/NSTEMI and STEMI populations.

1.3.1 Does the Committee agree that these findings are sufficiently robust and the two populations are sufficiently related to support an overall claim for the ACS patient population?

Consensus… Yes, the claim can be made for entire ACS population. There is no reason to have two separate indications.

1.3.2 Do the results support a superiority claim for prasugrel to the approved regimen of clopidogrel?

Consensus… Yes

2. Risk

The primary risk was bleeding, which was clearly worse on prasugrel.

What are the long-term consequences of non-fatal hemorrhage?

Unknown…It depends on the cause of the bleeding and the location of the bleed, if it is treatable by transfusion and the long term consequences of transfusions. Study participants who survived had similar outcomes.

2.1.2 In both treatment groups, bleeding was most frequent around the time of the index PCI, and much more frequent following CABG. All types of bleeding were more frequent on prasugrel than clopidogrel. Can patients likely to require CABG be identified prior to dosing? If so, should prasugrel be withheld in such patients?

Yes, if there is time to determine the anatomy.

Prference should be given to the use of prasugrel only following coronay angiography, as it was in the study, so that coronary anatomy is known, to allow assessment of the likelihood of requiring coronary bypass surgery; however, there should be guidance for physicians to make their decision including information about bleeding, particularly peri-operative bleeding for the situations where the anatomy cannot be determined before a decision has to be made.

2.1.3 Prior stroke/TIA. Fewer than 4% of subjects enrolled with prior stroke/TIA. Those randomized to clopidogrel had primary end point events about as often as did clopidogrel subjects with no such history. However, prasugrel subjects with a history of stroke/TIA had primary end point events nearly twice as often as other prasugrel subjects, and the risk of a subsequent stroke was much higher in prasugrel subjects with a history of stroke or TIA. Should labeling discourage use of prasugrel in patients with a history of stroke/TIA or in whom stroke/TIA develop during treatment with prasugrel?

All members agreed that prasugrel should not be used in these patients.

2.1.4 Weight. Quintile analyses of primary end point events reveal a fairly uniform advantage of prasugrel over clopidogrel regardless of weight, and suggest no strong relationship between weight and bleeding risk. In

contrast, a dichotomous analysis demonstrates a statistically significant increase in bleeding risk for patients <60 kg. What, if anything, should labeling say about use of prasugrel in patients according to weight?

Various opinions were rendered. There was agreement that some information should be provided. Some of the suggestions include: information about the risk for bleeding, PK data, consideration of decreasing the dose, and adding information when available from the Trilogy Trial.

2.1.5 Use with GPIIb/IIIa inhibitors. GPIIb/IIIa inhibitors were used by about half of all ACS subjects in TRITON. The clinical benefit of prasugrel on the primary end point was similar regardless of GPIIb/IIIa inhibitor use, and the risk of bleeding, although higher with GPIIb/IIa use, was not disproportionately worse on prasugrel. What, if anything, should labeling say about use of prasugrel in patients according to concomitant GPIIb/IIIa inhibitor?

Many of the members stated that nothing needed to be included. It was suggested that a statement of no effect would be informative and that the increase in TIMI major bleeding with extended use of the inhibitors should be mentioned.

2.1.6 Age. For patients in older age strata, while bleeding was not disproportionately worse on prasugrel, fatal hemorrhage was more common with prasugrel (1% vs. 0.1%), and prasugrel showed less benefit over clopidogrel. In addition, older ACS patients in the Study CURE received less benefit from clopidogrel over placebo. What, if anything, should labeling say about use of prasugrel in patients according to age?

Members seemed to be in agreement that a caution is warranted. Labeling should indicate that elderly may have greater risk with declining age with lower benefit; warning about, but no tbarring use. There was agreement that it is difficult to draw a "hard line" at any one age.

Comorbidity analysis may be helpful, for example; the benefit for diabetic patients was substantial.

2.2 Cancer was somewhat more commonly reported in the prasugrel group than in the clopidogrel group. The strength of association depends largely on whether or not non-melanoma skin cancers are included in the analyses. The pharmacologist and the Carcinogenicity Assessment Committee interpret the preclinical data as not indicative of carcinogenic or tumor growth enhancement. The Division of Oncology Drug Products consultative review concludes that the trend in TRITON was probably spurious. Although the review team has a range of views on the implications of these data, there is agreement that there should be some description in labeling. Does the Committee recommend

…a section in Warnings and Precautions?
…a box warning?
…a restriction on use for a limited time?
Almost all were in agreement that the information should be in the adverse reactions section and a few stated a need for further study.

2.3 The prasugrel batches used in TRITON contained varying ratios of salt to free base. In subjects not taking a proton pump inhibitor (PPI), salt and base produce the same exposure. However, at high gastric pH (as on a PPI), prasugrel base produces a lower maximum exposure to its active metabolite. In TRITON, about 41% of subjects were on a PPI at some time, and the benefit of prasugrel was similar in strata using and never using a PPI, and in strata based on prasugrel lot. Bleeding risk was somewhat higher in subjects on a PPI in both treatment groups, but the relative risk for bleeding on prasugrel compared with clopidogrel was similar in subjects taking a PPI (HR=1.1) and in those never taking a PPI (HR=1.2). To-be-marketed prasugrel is expected to contain less base than was in batches used in TRITON. What, if anything, should labeling say about this formulation issue?

Consensus… Nothing should be put in the label.

3. Risk-benefit

3.1 The cardiovascular event risk-benefit relationship is shown above. Even if the risks of hemorrhage could not be mitigated, does the Committee believe that this represents a favorable benefit to risk relationship?

Consensus…Yes

3.2 Does the Committee believe that the following restrictions are likely to improve the benefit to risk:

3.2.1 Avoiding use around CABG and other surgical or invasive procedures

Consensus…Yes, some guidance to inform physicians of the increased risk needs to be provided. In addition the agency should see if they can come up with a time frame as to when prasugrel should be avoided relative to surgical/invasive procedures.

3.2.2 Avoiding use in patients with prior stroke/TIA (and discontinuing use in patients who develop a stroke/TIA)

Consensus…Yes

One member suggested a box warning.

3.2.3 Avoiding use or lowering the dose in low-weight patients

Consensus… some guidance to inform physicians of the increased risk needs to be provided.

Four members supported including the suggestion of a lower dose.

3.2.4 Avoiding use in elderly patients?

Consensus… some guidance, to inform physicians of the increased risk, needs to be provided.

3.3 VOTE: Should prasugrel be approved to treat patients with acute coronary syndromes, presenting with either UA/NSTEMI or STEMI? After the vote, please comment.

Yes 9, No 0, Abstain 0