DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993

US Mail address:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Transmitted via e-mail:	Elizabeth Bearby, Ph.D.
Company Name:	Eli Lilly
Phone:	(317) 276-1203
Subject:	**Minutes of a meeting w/FDA on December 12, 2008 NDA 22-307**
Date:	January 13, 2009
Pages including this sheet:	6

From:	**Meg Pease-Fye, M.S.**
Phone:	**301-796-1130**
Fax:	**301-796-9838**
E-mail:	**meg.peasefye@fda.hhs.gov**

Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Meeting with Eli Lilly

Application Number:	NDA 22-307 IND 63,449
Sponsor:	Eli Lilly
Drug:	Effient (Prasugrel)
Meeting Date:	December 12, 2008
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Recorder:	Meg Pease-Fye, M.S.

List of Attendees:

Division of Cardiovascular and Renal Products

Ellis Unger, M.D.	Deputy Office Director, ODE I (acting)
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Thomas Marciniak, M.D.	Team Leader, Medical Officers
Karen Hicks, M.D.	Medical Officer
Edward Fromm, R. Ph.	Chief, Project Management Staff
Meg Pease-Fye, M.S.	Regulatory Health Project Manager

Eli Lilly

Cheryl Anderson, Pharm.D.	Director, U.S. Regulatory
Elizabeth Bearby, Pharm.D.	Scientific Director, Regulatory
Peter Morrow	Principal Regulatory Scientist, Regulatory
William Macias, M.D.	Director, Medical Director
Jeff Riesmeyer, M.D.	Fellow, Medical

Daiichi Sankyo

Rich Cuprys	Executive Director, Regulatory
James Molt, Ph.D.	Vice President, Global Regulatory
Howard Hoffman, M.D.	Vice President, Regulatory

BACKGROUND

A new NDA for prasugrel (22-307) was submitted to the Agency on December 26, 2007 for priority review (original PDUFA goal date: June 26, 2008). On June 20, 2008, a major amendment was submitted, extending the review clock by 3 months (new PDUFA goal date: September 26, 2008). Eli Lilly and Daiichi-Sankyo jointly seek an indication for the reduction of atherothrombotic events and stent thrombosis in ACS patients with unstable angina or NSTEMI (non ST-segment elevation myocardial infarction) who are managed with percutaneous coronary intervention (PCI) and patients with STEMI who are managed with primary or delayed PCI. This NDA is supported primarily by the TRITON-TIMI-38, a Phase 3, multi-center, randomized, parallel-group, double-blind, double-dummy, active-controlled study, with clopidogrel as the active comparator.

The issues that have raised Agency concern are:

- **Formulation**: Prasugrel was included in the Quality by Design (QbD) pilot program. Lilly initiated prasugrel development using a free base of the drug substance, but determined that the hydrochloride (HCl) salt had better bioavailability at higher gastric pH. Because a substantial fraction of the patients on anti-platelet medications take proton pump inhibitors (PPI) to reduce gastric acidity and gastric bleeding, Lilly switched the manufacturing process to the HCl salt form of the drug substance, with the concurrence of the Division.

  Late in development, near the completion of the pivotal efficacy study, an acid-base reaction between the HCl salt and an excipient, [redacted], was discovered which converted up to 86% of the salt form to the free base. Conversion continued during storage up to 20 days and was affected by relative humidity and storage temperature. b(4)

- **Risk of bleeding**: Bleeding events are higher and specific information is merited in labeling for:

  1. patients ≥ 75 years of age (greater risk is for fatal and life-threatening bleeding)
  2. patients with a prior history of a transient ischemic attack or cerebrovascular accident (contraindication)
  3. patients who undergo CABG, or, probably any surgical procedure

  The trade-off between efficacy and bleeding is largely between prevention of non-fatal myocardial infarction versus causation of transient morbidity and the Division currently believes that this is a worthwhile trade for patients who might receive prasugrel.

- **Neoplasia**: Lilly contends that the higher incidence of non-benign neoplasms observed in prasugrel-treated subjects resulted from ascertainment bias due to the higher incidence of bleeding in prasugrel-treated subjects.

The objective of this meeting was to discuss advisory committee meeting topics. The Division confirmed that an Advisory Committee meeting is planned. Assuming that the February 3, 2009 date is accurate, Lilly's briefing document for an advisory committee meeting is due to the FDA at the end of December. Lilly wants to be certain that the appropriate topics are discussed for the committee. FDA agreed that it is important to have continued discussions prior to the potential date.

DISCUSSION

The following topics were discussed as potential items for discussion at the Advisory Committee.

Formulation:

Lilly is concerned about proprietary issues related to the formulation of the product. If formulation is to be a topic for public discussion, they would like a closed committee meeting. FDA is evaluating whether or not a portion of the meeting will be closed and the Division remains uncertain at this point when a decision will be made. Specific questions to ask the AC panel have not yet developed by the Division.

The Division stated that there are no chemists on the Advisory panel, so the discussion will focus on the clinical implications of shifting from the studied formulation to the proposed marketed formulation (a completely salt conversion). The concern is about subsequent bioavailability and the Division does not intend to delve into the manufacturing process. The product, as studied, is an issue of approval; any post-marketing commitment discussions will not be public.

Action Item: FDA expects that only summary information should be necessary and asked Lilly to submit a list of topics related to the formulation that would necessitate a closed session, as well as a list of topics that would be acceptable to discuss in an open session.

Note: This was subsequently submitted to the Division on December 16, 2008.

Neoplasia:
FDA indicated that if the sponsors present their case that neoplasm is not a public concern based solely on their idea of "detection bias," the Division will refute it. Lilly needs to present their case as to why there should not be a concern about the neoplasm data and should be prepared to defend how they counted tumor cases (inclusion of skin) and how the mortality was interpreted. The Division still remains unclear as to how to describe these tumors in labeling. When Lilly asked if agreement with respect to describing neoplasia in labeling would preclude the need for an AC discussion, the Division responded that this topic must be discussed at an AC, but if we agree on labeling language then that would be noted.

As to the most recent neoplasm submission, the Division still has not yet completed its review; however there are still differences of opinion with a few of the neoplasm cases; these should be resolved prior to the meeting. The Division and the sponsors agreed that it would be preferable to avoid presentation of specific cases, and preferable if the numbers of cases identified by the Division and sponsors agree.

Action Item: FDA will provide a listing of how the outstanding few cases were counted that differed from the October 29, 2008 meeting between the FDA and sponsors. [In post-meeting communications, the FDA provided Lilly with a listing of disputed cases; Lilly declined to discuss the cases further and stated the intention to footnote the differences of opinions.] FDA will present the data on how the differences in all cause mortality in cancer patients should be interpreted.

Bleeding (Risk/Benefit):
The Division again unequivocally stated that their position has not changed and the Advisory Committee meeting will be used as a forum for transparency. The benefit outweighs the risk for specific populations and those populations that are contraindicated are clearly identified and will be clearly labeled. The committee will only be asked to vote on the overall benefit risk and the overall approvability of the molecule.

It is likely that the Division will require a boxed warning in the labeling and that it will definitely include the contraindicated populations (prior TIA/Stroke) although there will also be a focus on overall bleeding risk, and possibly the elderly.

Dose adjustment:
There is still internal FDA discussion as to a recommendation for 5 mg to be considered for the lower weight patients and the elderly. This topic may be discussed at the committee meeting. While prasugrel is likely to reduce the risk of bleeding with a lower dose, FDA questions whether the benefit will be lessened.

Action Item: FDA requested a copy of the additional analyses related to dose adjustment and to be kept apprised of the EU application.

Other Discussion Items:

- The Division is still unclear as to whether OSE (Office of Surveillance and Epidemiology) intends to present at the advisory committee meeting, but Lilly should be prepared for the eventuality. Further, any FDA reviewer who wishes to present will be allowed to do so.

- Stent thrombosis data and the readjudication process may still be a part of the risk benefit discussion. The Division has not yet completed its review of the data submitted last Friday.

- There will be continued efforts to revise labeling up to the committee meeting.

- Updates on major regulatory actions in the EU regarding prasugrel will continue to be submitted to the NDA.

- A specific timeline for completing the review is not established since the PDUFA action date was missed. FDA intends to complete the review shortly after the AC, but this depends on the outcome of that meeting. The Division is interested in resolving this matter as rapidly as possible after the AC meeting.

Date Minutes Drafted: January 5, 2009
Date Minutes Finalized: January 13, 2009

Recorder: *{See appended electronic signature page}*
Meg Pease-Fye, M.S.

Chair Concurrence: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

N. Stockbridge 01.13.2009
E. Unger 01.12.2009
K. Hicks 01.12.2009
T. Marciniak 01.06.2009
E. Fromm 01.06.2009

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/s/

Margaret Pease-Fye
1/13/2009 08:29:04 AM

Norman Stockbridge
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