

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
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Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266**

Transmitted via e-mail: Elizabeth Bearby, Pharm.D.

Company Name: Eli Lilly

Phone: (317) 276-1203

Subject: Minutes of a meeting w/FDA on
November 4, 2008
NDA 22-307

Date:

Pages including this sheet:

From: Meg Pease-Fye, M.S.

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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: November 4, 2008

Meeting Chair: Mohab Nasr, Ph.D.
Recorder: Meg Pease-Fye, M.S.

Attendees:

Office of New Drug Quality Assessment

Mohab Nasr, Ph.D.	Director
Blair Fraser, Ph.D.	Director, Division of
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead
Sharmista Chatterjee, Ph.D.	Chemistry/Manufacturing Sciences Reviewer
Zengfang Ge, Ph.D.	Chemistry Reviewer
Patrick Marroum, Ph.D.	Clinical Pharmacology Reviewer
Rebecca McKnight	Regulatory Project Manager

Division of Cardiovascular and Renal Products

Ellis Unger, M.D.	Deputy Director
Karen Hicks, M.D.	Medical Officer
Albert DeFelice, Ph.D.	Pharmacology/Toxicology
Belay Tesfamariam, Ph.D.	Pharmacology/Toxicology
Meg Pease-Fye, M.S.	Regulatory Health Project Manager

Eli Lilly

Elizabeth Bearby, Pharm.D.	Senior Scientific Director, Regulatory
Gregory C Davis, Ph.D.	Executive Director, Regulatory CMC
Mark A Kryah	Manager, Project Management CMC
Ralph Lipp, Ph.D.	Vice President, Pharmaceutical Sciences
William Macias, M.D.	Medical Director for prasugrel
Lan Ni, Ph.D.	Head, Pharmacokinetics
_____ Ph.D.	Advisor, Regulatory CMC

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Daiichi Sankyo

Paulette Kosmoski	Executive Director, Regulatory Affairs, CMC
Dan Salazar, Ph.D.	Vice President, Translational Medicine and Clinical Pharmacology

BACKGROUND

An NDA (22-307) for prasugrel was submitted to the Agency on December 26, 2007 for priority review. 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, a Phase 3, multi-center, randomized, parallel-group, double-blind, double-dummy, active-controlled study, with clopidogrel as the active comparator.

Several issues have raised Agency concern, and this meeting was held specifically to address continuing developments concerning formulation. Prasugrel was selected to be in the Quality by Design (QbD) pilot program initiated by CDER. Lilly began prasugrel development using a free base of the drug substance, but later determined that the hydrochloride (HCl) salt had better bioavailability at higher gastric pH. 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, Lilly discovered that _____ converted up to 86% of the salt form to the free base. Conversion continued during storage up to _____ the mechanism of this conversion was likely discovered as a result of following the science-based drug development approach encouraged under the Quality by Design paradigm of drug development. The extent to which this type of conversion may occur with other products is unknown and its clinical relevance is also unknown, but relative humidity and storage temperature do affect the conversion. The Agency finds the large variability very troubling. Salt to base conversion occurs regardless of whether or not a patient is on a proton pump inhibitor; however, in addition to the salt to base conversion issue, there is an additional concern about patients on prasugrel who take proton pump inhibitors (PPI) to reduce gastric acidity and gastric bleeding. Study H7T-EW-TACS in healthy volunteers receiving lansoprazole demonstrated that high (70%), intermediate (58%), and low (5%) conversion prasugrel tablets (60 mg) were bioequivalent.

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DISCUSSION

After introductions, Lilly presented to the Agency their strategy _____

_____ They showed the following slides:

10 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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ACTION ITEMS

- No additional information is necessary at this time. The Agency will hold internal discussion as to the impact of the current conversion on review status.
- Lilly will provide additional information about pharmacokinetic data, how those data were obtained, and how they support their conclusions regarding conversion.
- Lilly will supply additional information as to the absorption of the molecule.

Date Minutes Drafted: November 24, 2008
Date Minutes Finalized:

Recorder: {See appended electronic signature page}
Rebecca McKnight

Chair Concurrence: {See appended electronic signature page}
Mohab Nasr, Ph.D.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Moheb Nasr
12/12/2008 11:30:32 AM

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Transmitted via e-mail: Elizabeth Bearby, Ph.D.

Company Name: Eli Lilly

Phone: (317) 276-1203

Subject: Minutes of a meeting w/FDA on
September 24, 2008
NDA 22-307

Date: November 13, 2008

Pages including this sheet: 7

From: Meg Pease-Fye, M.S.
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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: September 15, 2008

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Recorder: Meg Pease-Fye, M.S.

List of Attendees:

Division of Cardiovascular and Renal Products

Robert Temple, M.D.	Director, Office of Drug Evaluation I
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Ellis Unger, M.D.	Deputy Director
Karen Hicks, M.D.	Medical Officer
Albert DeFelice, Ph.D.	Pharmacology/Toxicology
Belay Tesfamariam, Ph.D.	Pharmacology/Toxicology
Rajnikanth Madabushi, Ph.D.	Office of Clinical Pharmacology
Allen Brinker, M.D.	Office of Surveillance and Epidemiology
Mary Willy	Office of Surveillance and Epidemiology
Diane Wysowski, Ph.D.	Office of Surveillance and Epidemiology
Monika Houstoun, Pharm. D.	Office of Surveillance and Epidemiology
Gita Akhavan-Toyserkani, M.B.A., Pharm.D.	Office of Surveillance and Epidemiology
Meg Pease-Fye, M.S.	Regulatory Health Project Manager

Eli Lilly

Jennifer Stotka, M.D.	Vice President, U.S. Regulatory Affairs
Cheryl Anderson, Pharm.D.	Director, U.S. Regulatory
Elizabeth Bearby, Pharm.D.	Scientific Director, Regulatory
Norma Ascroft, Pharm.D.	Scientific Director, Regulatory
J. Anthony Ware, M.D.	Vice President, Cardiovascular Platform Leader
William Macias, M.D.	Director, Medical Director
Jeff Riesmeyer, M.D.	Fellow, Medical
Javan Collins	Prasugrel Team Leader
Govinda Weerakkody, Ph.D.	Advisor, Statistician

Daiichi Sankyo

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, a Phase 3, multi-center, randomized, parallel-group, double-blind, double-dummy, active-controlled study, with clopidogrel as the active comparator.

Several issues have developed that have raised Agency concern:

- **Formulation:** prasugrel was one of the NDAs included in the Quality by Design (QbD) pilot

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- **Risk of bleeding:** Bleeding events are higher and specific information is merited in labeling for:
 1. patients \geq 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 tradeoff 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.

Lilly has requested a series of regular meetings to keep them apprised of the review process. This is the second. They wish to touch base with Agency thinking about:

- _____
- Missing the Goal Date: what are the ramifications?
- Ascertainment Bias: Did anemia lead to a greater search for cancers and what is the nature of the disagreement for the respiratory tumors?

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- Details concerning the proposed Active Surveillance Plan (risk management), particularly during the TRILOGY study

DISCUSSION

After introductions, Lilly made comments pertaining to the biologic plausibility of early detection of tumors. Dr. Stockbridge reminded Lilly that no one in the Division believes that prasugrel is a carcinogen, although there may be some concern that it makes existing tumors grow. Lilly is still unable to determine a mechanism that could explain how this drug might stimulate tumor development. Subjects with neoplasms reported at baseline were eligible for study enrolment, but neoplasms extant at the time of study entry were to be recorded in the CRFs as pre-existing conditions only if they were active (*i.e.*, “ongoing” at the time of enrolment).

Dr. Unger asked whether prasugrel had been screened for pro-angiogenic effects in *in vitro* cell culture models. Lilly stated that difficulties arise because ADP receptors that inhibit platelets tend to decrease angiogenesis, metastases and tumor growth. Dr. Unger noted that the company seems to be making the assumption that the drug could influence tumor development only through its effects on platelets, whereas it might have direct effects on tumor cells or angiogenesis, independent of platelets.

Lilly still disagrees with the Agency as to which tumors to include in the analysis (and subsequent labeling) and which to exclude, specifically, the non-melanoma skin (squamous and basal cell), arguing that the tumor animal models are not useful in predicting human results. Dr. Temple stated that he believes that both should be included.

Lilly noted that they and the Division are close to agreement on subject tumor classification. Only a re-analysis of the causative events is needed (*i.e.*, when a bleed in GI and GU triggered further examination and subsequent discovery of tumor). When asked about anemia findings, Lilly stated that they removed all anemia events (they are not included as “bleeds”). Dr. Unger stated that he sees 2 outstanding issues:

- Lilly still asserts that ascertainment bias largely accounted for the difference in cancer frequencies
- Lilly continues to include non-melanoma skin in their analyses

With regard to ascertainment bias, Dr. Unger argued that if the antecedent cancers were not considered and only those cancers without bleeding events are considered, the relative risk is ~1.35. Dr. Unger noted special concern regarding the role of anemia in ascertainment bias. The Division accepts the argument that prasugrel caused excess bleeding adverse events relative to clopidogrel, which could have led to additional clinical evaluations and diagnoses of cancer in the prasugrel group (ascertainment bias). On the other hand, the Division disagrees that the development of anemia as an adverse event, in the absence of bleeding, should be attributed to prasugrel, unless in an organ system where there is the potential for occult bleeding, *i.e.*, gastrointestinal (GI) and genitourinary (GU) tumors. Although anemia as an adverse event might play a role in the diagnosis of a number of cancers, it is not appropriate to attribute the anemia to prasugrel in the absence of a bleeding adverse event. Although pulmonary tumors can cause bleeding, generally such bleeding (hemoptysis) would not be occult. Therefore, anemia (without a bleeding adverse event) could be a source of ascertainment bias for GI and GU tumors, but not for tumors in organ systems where bleeding is not a typical symptom (*e.g.*, breast, prostate, central nervous system, etc...), or for pulmonary tumors.

The sponsor largely accepted and agreed with Dr. Unger's assertions regarding anemia and ascertainment bias.

If the anemia is not included, the relative risk becomes ~1.44. Dr. Unger opined that Lilly does not make their case that the imbalance is due to ascertainment bias, since elimination of these cases does not make the signal go away.

Lilly stated that they consider the absolute differences, which depend on how the non-melanoma skin cancers are considered. Dr. Unger stated that at this point, we need to agree to disagree on this issue, in that the Division considers both analyses (with and without non-melanomatous skin cancers) to be important.

Lilly again asked the Division why the non-melanoma skin was excluded in their analysis and Dr. Unger noted that clinically these tumors are readily curable without important health consequences, and generally considered in a separate category. Dr. Temple added that the question is only about what the label will say since the Agency will not remain silent on this issue. Dr. Unger added that the data are not compelling that there is a causative effect, but the Agency remains concerned.

Drs. Temple and Stockbridge shared the necessity for bringing prasugrel before an Advisory Committee. The new legislation, FDAAA, is very clear that all new molecular entities should go before an Advisory Committee unless there is a compelling reason why they should not. Further, Dr. Stockbridge noted that the Cardio-Renal Advisory Committee will not be meeting again in 2008, although he will endeavor to get one convened at the earliest available opportunity.

Lilly asked for an idea of the review process at this point. Dr. Temple noted:

- The PDUFA date will be missed. No action letter will go out.
- We cannot pursue labeling yet, since we do not know the outcome of the outstanding issues, although we do know there will be a boxed warning which will clearly define the populations that should not take prasugrel (TIA/stroke, ≥ 75 years, patients undergoing CABG or other procedures, particular concomitant medicines).
- White papers are being written and then these will be presented to senior management. These papers are intended to compile all arguments and present a balance of opinion.

Lilly again offered to meet with the senior management and asked to set up the next meeting in order to discuss REMS and risk management strategies. Dr. Unger responded that the Agency is unable to write specific Post-Marketing Requirements at this point, without additional input from management on the conversion issue. When Lilly asked about a separate, closed Advisory Committee for CMC issues, Dr. Temple responded that we are unsure at this time and cannot make a comment either way. Dr. Unger added that the Agency is still considering what the duration of treatment should be (*i.e.*, whether length of treatment should be limited).

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ACTION ITEMS

- Lilly will specify for the Division the location of the pharmacodynamic data in the application comparing the rat to the human.

Date Minutes Drafted: September 30, 2008

Date Minutes Finalized: November 13, 2008

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

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

**This is a representation of an electronic record that was signed electronically and
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/s/

Margaret Pease-Fye
11/13/2008 02:04:52 PM

Norman Stockbridge
11/14/2008 08:50:47 AM