

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 22, 2008

NDA #: 22-307

DRUG NAMES: Effient (prasugrel)

APPLICANT: Eli Lilly

BACKGROUND:

Prasugrel is a thienopyridine, third product in this class after:

- ticlopidine hydrochloride (NDA 19-979) originally approved in October, 1991 and is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors in patients who have had a completed thrombotic stroke, based on the STARS (Stent Anticoagulation Restenosis Study) study approved on April 18, 2001 and for adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation based on ISAR (Intracoronary Stenting and Antithrombotic Regimen Trial) data
- clopidogrel bisulfate (NDA 20-869) originally approved on November 17, 1997, based on the CAPRIE study, for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease. On February 27, 2002, Plavix was approved for Acute Coronary Syndrome (ACS) based on the findings of the CURE study. This supplemental application proposes a new indication for Plavix in patients with ST-elevation myocardial infarction (STEMI), based on the findings of the COMMIT and CLARITY studies.

Eli Lilly and Daiichi-Sankyo are seeking an indication for the reduction of atherothrombotic events and stent thrombosis in ACS patients with unstable angina or NSTEMI who are managed with PCI and patients with STEMI who are managed with primary or delayed PCI. This NDA is supported primarily by the TRITON-TIMI study.

ATTENDEES:

Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products

Ellis Unger, M.D., Deputy Director, Division of Cardiovascular and Renal Products

Thomas Marciniak, M.D., Team Leader, Medical Officers

Karen Hicks, M.D., Medical Officer

Elena Mishina, Ph.D., Office of Clinical Pharmacology

Rajnikanth Madabushi, Ph.D., Office of Clinical Pharmacology

Albert DeFelice, Ph.D., Team Leader, Pharmacology

Belay Tesfamariam, Ph. D., Pharmacology

Kasturi Srinivasachar, Ph.D., Team Leader, Office of New Drug Quality Assessment

Sharmista Chatterjee, Ph.D., Team Leader, Office of New Drug Quality Assessment

Zhengfang Ge, Ph.D., Office of New Drug Quality Assessment

Rebecca McKnight, Project Manager, Office of New Drug Quality Assessment

James Hung, Ph.D., Director, Office of Biometrics I

Cherry Liu, Ph.D., Statistician, Office of Biometrics I

Federico Goodsaid, Ph.D., Genomics, Office of Translational Sciences
 Mary Dempsey, Office of Surveillance and Epidemiology
 Gita Akhavan-Toyserkani, Office of Surveillance and Epidemiology
 Edward Fromm, R.Ph., Chief, Project Management Staff
 Meg Pease-Fye, M.S., Regulatory Health Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting):

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Karen Hicks
Secondary Medical:	Thomas Marciniak/Ellis Unger
Statistical:	Cherry Liu
Pharmacology:	Belay Tesfamariam
Statistical Pharmacology:	Atiar Mohammad Rahman
Chemistry:	Kasturi Srinivasachar
Environmental Assessment (if needed):	
Biopharmaceutical:	Elena Mishina
Microbiology, sterility:	Not Applicable
Microbiology, clinical (for antimicrobial products only):	Not Applicable
DSI:	consulted February 1, 2008
OPS:	
Regulatory Project Management:	Meg Pease-Fye
Other Consults:	QT, consulted January 2, 2008 Pediatrics, consulted February 8, 2008 Risk Map, consulted January 31, 2008 Genomics, consulted October 2, 2007 Tradename, consulted January 10, 2008

Per reviewers, are all parts in English or English translation? YES NO

CLINICAL FILE REFUSE TO FILE

• Clinical site audit(s) needed? YES NO

• Advisory Committee Meeting needed? YES, date if known _____ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
 N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

• Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

• GLP audit needed? YES NO

CHEMISTRY

FILE

REFUSE TO FILE

- Establishment(s) ready for inspection?
- Sterile product?

YES NO
YES NO

ELECTRONIC SUBMISSION:
No comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):
 - Physician's Labeling Rule format comments

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Meg Pease-Fye, M.S.
Regulatory Project Manager

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/s/

Margaret Pease-Fye
2/28/2008 09:48:48 AM
CSO



NDA 22-307

NOTICE OF POTENTIAL FILING ISSUES

Eli Lilly and Company
Attention: Elizabeth C. Bearby, Pharm.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Bearby:

Please refer to your December 26, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effient (prasugrel) Tablets.

We also refer to your submission dated January 15, 2008.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Your "Regulatory Response Questions from January 3, 2008 Meeting explains in Table 1, Annotated CRF Page Number 2 that the question "Did the subject meet all Protocol Eligibility Criteria?" was not used in any analyses but was used for data management. Please provide a dataset with this variable.
2. Please provide datasets with the five variables discussed in Topic 2 of your "Regulatory Response Questions from January 3, 2008 Meeting," dated January 15, 2008.
3. Three dates regarding study drug administration (loading dose, first maintenance dose, and last dose of study drug) were listed on the original CRFs as "not entered" and the original DEFINE.PDF file did not include variables referencing these fields. Table 1 explains that these variables were "not appropriately annotated in the aCRF provided in the original submission." However, the referenced variables that have been changed from "derived" do not appear to contain the raw data. For example, the reference for "Date of last dose of study drug," CRF page 28, is the variable SDYTRT/SDYTRTEC. This variable has no missing values. However, the very first CRF examined, for site 010001, subject 11390 has "-- JAN 2006" entered for this field. The SDYTRT/SDYTRTEC value is "2006-01-31". This variable must be a derived variable. Please provide datasets with the raw values for all three dates.
4. The explanation for the "not entered" for the question "Are there new pathological Q waves that are not related to a prior known event," CRF Page Number 18, refers to variables that reference only CRF pages 7 and 25. Please provide a dataset with the response to the question from page 18.
5. Your DEFINE.PDF describes a variable "TRT1" in the CVTREAT.XPT dataset described as "set equal to the variable TRT from the randomization dataset (from the Interactive Voice Randomization System)." Please provide a copy of this randomization dataset and a DEFINE.PDF for it.
6. The HEADER dataset has a variable RANDDTM that is described as "Derived. Hard-coded from the study randomization table." Please explain what the "study randomization table" is and provide a copy of it if not already submitted. Why is this variable not taken from the randomization dataset?
7. As the previous questions and responses confirm, there is continuing confusion in your submissions regarding what are the raw data and what are derived or related data. We believe the easiest way to clear up the confusion regarding the raw data is for you to submit SAS data sets corresponding to the entry datasets for all of the CRFs without any transformations or derivations. The requirement to submit raw datasets

NDA 22-307
Effient (prasugrel) Tablets

was discussed at the pre-NDA meeting. Please provide also a DEFINE.PDF for these data sets, an annotated CRF referencing them, and a document explaining how your primary and secondary efficacy analyses and your major safety analyses are derived from the raw data.

8. Please submit the raw data for the following in vitro studies: 2002IV-HI01, 2002IV-DI002, 2002IV-DI003, 2003IV-EI001, 2007IV-EI002, and 2007IV-PG001

In order to insure timely filing of this application, we need the above data submitted within one week. If you have any questions, please call Meg Pease-Fye, Regulatory Health Project Manager, at (301) 796 -1130.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
1/25/2008 02:06:08 PM



NDA 22-307

NDA ACKNOWLEDGMENT

Eli Lilly and Company
Attention: Elizabeth C Bearby, Pharm.D.
Scientific Director, US Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Bearby:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: EFFIENT (prasugrel hydrochloride) Tablets

Date of Application: December 26, 2007

Date of Receipt: December 26, 2007

Our Reference Number: NDA 22-307

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 26, 2008 in accordance with 21 CFR 314.101(a).

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however,

it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please contact:

Ms. Meg Pease-Fye, M.S.
Regulatory Health Project Manager
(301) 796-1130

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
12/28/2007 09:29:11 AM



IND 63,449

Eli Lilly and Company
Attention: Elizabeth C. Bearby, Pharm.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Bearby:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Prasugrel (CS-747).

We also refer to your amendments dated September 18, 2007 (serial # 481), February 26, 2005 (serial # 103), May 11, 2005 (serial # 134), August 12, 2005 (serial # 177), and May 17, 2007 (serial # 443), containing the statistical analysis plan and multiple amendments for study TAAL, entitled, "The Effect of Interaction of CYP450/Drug Metabolizing Genotype with Prasugrel and Clopidogrel Treatment on Efficacy Outcomes in Patients with Acute Coronary Syndrome who are to Undergo Percutaneous Coronary Intervention." Finally, we refer to your amendment dated September 18, 2007 (serial # 482) containing your proposed statistical analysis plan for the integrated summary of safety.

We have completed the statistical review of your submissions and have the following comments and recommendations.

Statistical Analysis Plan for TAAL:

We have provided comments on the formal statistical analysis plan of the TAAL trial in the past. The primary study objective of this trial is to test the hypothesis that CS-747 plus aspirin is superior to clopidogrel plus aspirin in the treatment of subjects with acute coronary syndrome (ACS) who are to undergo percutaneous coronary intervention (PCI). You did not provide adequate details on this genomic analysis plan if the results of the analyses are intended to be reported in the labeling. Given the events described above and below, these analyses should be considered as exploratory analyses at this stage.

The participation in the sample collection for the DNA extraction was voluntary for patients who participated in the trial. The population that the genomic statistical analyses are based upon is no longer an ITT population.

Repetitively analyzing the primary endpoint on various subgroups can significantly increase the probability of observing false positive results. The genotyping in the genomic statistical analyses involves multiple ways of categorizing patient groups in those voluntarily consented patients. Such analyses might help generate hypotheses for future study planning.

It is not clear to us how the variant data are translated/classified to the common consensus allele. The proposal did not address this issue with adequate details. The classification algorithm seems to be able to lead to different results from the same data. For example, in Table 2 in the appendix of Genetic Methods and Data Acquisition, the phenotypes for CYP2C19 are predicted based on the SNP in DME/T chip but the conditions are not mutually exclusive. Since CYP2C19 (and 2C9) can be categorized to more than one phenotype based on the SNP, it is not clear to which subgroup will the patient be classified.

The data obtained from molecular experiment can have large variability. It will be helpful if sample extract from each patient has replicates to ensure the reproducibility. Validation of the classification should also be conducted to estimate the misclassification rate of the metabolic status from genotyping.

The proposal should include more details on quality control. Numerous factors can affect the laboratory results, for example, but not limited to, samples collected at different times/sites, or processed by different methods or by different technicians.

Statistical Analysis Plan for the Integrated Safety Analysis

This submission only describes analyzing 30 days from safety from TAAL versus other studies. All available safety data from TAAL must be analyzed as well.

If you have any questions, please call:

Meg Pease-Fye, M.S.
Regulatory Health Project Manager
(301) 796 -1130

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name

IND 63449

ELI LILLY AND CO

CS-747

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/s/

NORMAN L STOCKBRIDGE
11/27/2007