



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 22-307

Eli Lilly and Company
Attention: Elizabeth Bearby, PharmD
Scientific Director, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Bearby:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EFFIENT® (prasugrel hydrochloride).

We are reviewing the Chemistry, Manufacturing, and Controls 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.

In reference to the Post Approval Marketing Plan, we have the following comments:

The Agency is still in the process of determining the correct regulatory pathway that would allow us to approve a PMP, such as the one outlined in your NDA. Therefore, we will not be able to review the PMP if submitted as part of your NDA at this point. It is our intention to make public if and when we are ready to accept PMPs for review and approval. Lilly may consider the option of submitting comparability protocols in the NDA, which is currently permissible under the regulation and according to the FDA draft guidance on Comparability Protocols.

b(4)

In reference to the Drug Substance we have the following comments and questions:

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4 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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b(4)

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Please provide samples of the drug product. Samples may be sent to the following address:

Rebecca McKnight, RPM, ONDQA
CDER – White Oak
Building 21, Room 2667
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

In addition to submitting your responses to the NDA, please also send a copy via email to <rebecca.mcknight@fda.hhs.gov>. To facilitate the review process, we request that your responses be submitted in small groups rather than as one document. Please begin submitting your responses as soon as they are completed.

If you have any questions, contact Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Blair A. Fraser, Ph.D.
Director
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Blair Fraser
3/7/2008 05:17:42 AM

Executive CAC

Date of Meeting: 2/26/2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
John Leighton, Ph.D., DDOP, Alternate Member
Albert DeFelice, Ph.D., DCRP, Team Leader
Belay Tesfamariam, Ph.D., DCRP, Presenting Reviewer

Author of Minutes: Belay Tesfamariam, PhD

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 22-037
Drug Name: Prasugrel (CS-747)
Sponsor: Eli Lilly & Co., Indianapolis, IN

Background:

Prasugrel (CS-747) is a prodrug, member of the thienopyridine class that is de-esterified to form an active metabolite that irreversibly inhibits platelet P2Y₁₂ purinergic receptor, and thus prolongs bleeding times. All circulating metabolites in humans occurred in the circulation of the nonclinical species. No genetic toxicity was observed for prasugrel in standard tests that included an *in vitro* bacterial mutation test, Chinese hamster lung chromosomal aberration assay, and *in vivo* mouse micronucleus test.

Mouse Carcinogenicity Study:

The mouse carcinogenicity study was conducted at doses up to 300 mg/kg which yielded systemic exposures of prasugrel metabolites of about 500-fold greater than the anticipated clinical exposures. The doses were adequately high in that an MTD was achieved in the 300 mg/kg groups as indicated by body weight decreases of 9 - 11% of controls. Necropsy revealed treatment-related changes in the liver that may be related to the tumor and non-tumor lesions. Centrilobular hypertrophy and a tendency for an increase in the incidence of eosinophilic altered cell foci were observed suggesting that hepatic drug-metabolizing enzyme induction was involved in the liver lesions. Histopathology revealed an increase in the incidence of hepatocellular adenoma in males dosed at the high dose (300 mg/kg) and in females dosed at mid and high doses (100 or 300 mg/kg). Thus, there was an increased incidence of tumors (hepatocellular adenomas) in mice exposed for 2 years to high doses (190 times human exposure).

Rat Carcinogenicity Study:

The rat carcinogenicity study was conducted at doses up to 100 mg/kg which yielded systemic exposures of prasugrel metabolites greater than 50-fold than the anticipated clinical exposures. The doses were adequately high in that an MTD was achieved in the 100 mg/kg groups as indicated by body weight decreases of 11 - 13% of controls. Prasugrel did not induce treatment-related tumors in any of the organs/tissues. Prasugrel neither decreased the survival rate nor induced any specific tumor or non-tumor deaths. Necropsy revealed treatment-related changes in the liver, lung and trachea, and they were related to the non-tumor lesions which may be related to hepatic drug-metabolizing enzyme induction. Thus, in the rat there was no significant evidence of treatment-related tumors in a 2 year study with prasugrel exposures ranging to about 50 times the recommended therapeutic exposures in humans.

Executive CAC Recommendations and Conclusions:

Rats:

- * The Committee determined that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- * The Committee determined that the study was negative for drug related tumors.

Mouse:

- * The Committee determined that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- * The Committee determined that the study was positive for hepatocellular adenomas in both sexes.

David Jacobson Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DCRP
/Albert DeFelice, PhD, Team leader, DCRP
/Belay Tesfamariam, PhD, Reviewer, DCRP
/Meg Pease-Fye, CSO/PM, DCRP
/ASeifried, OND IO

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/s/

David Jacobson-Kram
2/27/2008 01:05:41 PM



NDA 22-307

PRIORITY REVIEW DESIGNATION

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 new drug application (NDA) dated December 26, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Effient, (prasugrel) 5mg and 10mg Tablets.

We also refer to your submissions dated January 15, 25, 28 and 30, and February 4, 6 and 19, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is June 26, 2008.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before March 9, 2008.

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

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/s/

Norman Stockbridge
2/21/2008 12:56:47 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for prasugrel.

We also refer to your amendment dated January 17, 2008, containing your proposed changes to the H7T-MC-TABY protocol, documented in your September 13, 2007 request (serial number 478) for a special clinical protocol assessment. The protocol is entitled, "A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed – the TRILOGY ACS Study."

We have completed our review and find your proposed changes acceptable; however, we have concerns regarding your proposed statistical analyses. As proposed, you may only obtain a labeling claim for patients < 75 years old. Your proposed secondary analysis, combining all age groups, may not alone support a claim for efficacy in all age groups or specifically for patients \geq 75 years old if the majority of the beneficial effect is seen in patients < 75. We suggest adding a third analysis, with conservation of alpha, only in patients \geq 75 years old. If a statistically significant effect is shown for this older subgroup, then you will have a strong argument for a claim in this subgroup and for all adult age groups provided that safety is acceptable. If the effects are not statistically significant in this older subgroup alone, we will still consider a claim for all age groups if a statistically significant effect is shown in the analysis of all age groups, the effect in the older age group is close to significant, and safety is acceptable, but the latter scenario would not be as compelling as a clear win for the older age group analyzed alone.

Additionally, we recommend that you record the duration of diabetes in the case report forms. For the efficacy and safety analyses, we suggest assessment of subgroups based on sex and use of glycoprotein IIb/IIIa inhibitors prior to catheterization. We also suggest analyses of efficacy

and safety by subgroups of use or non-use of proton pump inhibitors at baseline, and, for safety analyses, use or non-use of concomitant proton pump inhibitors at the time of the events.

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
02/19/2008

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-307 Supplement # 000 Efficacy Supplement Type SE-

Proposed Proprietary Name: Effient
Established Name: prasugrel hydrochloride
Strengths: 5 mg and 10 mg Tablets

Applicant: Eli Lilly
Date of Application: December 26, 2007
Date of Receipt: December 26, 2007
Date of Filing Meeting: January 22, 2008
Filing Date: February 24, 2008
Action Goal Date (optional):

User Fee Goal Date: June 26, 2008

Indication(s) requested: “
EFFIENT is indicated for the reduction of atherothrombotic events and the reduction of stent thrombosis in acute coronary syndromes (ACS) as follows:

- patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) who are managed with percutaneous coronary intervention (PCI).
- patients with ST-segment elevation myocardial infarction (STEMI) who are managed with primary or delayed PCI.

Prasugrel has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.”

Type of Original NDA: (b)(1) (b)(2)
Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: ID: 3007953 Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- Is the application affected by the Application Integrity Policy (AIP)? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
- Submission complete as required under 21 CFR 314.50? YES NO

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
 This application is: All electronic Combined paper + eNDA
 This application is in: NDA format CTD format
 Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 5 Years NO
- Correctly worded Debarment Certification included with authorized signature? YES NO

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO
- Financial Disclosure forms included with authorized signature? YES NO
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
- List referenced IND number: 63,449
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s) Date(s) August 4, 2004; January 25, 2005 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) May 30, 2007 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) October 1, 2004; October 19, 2007 NO

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to
DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for
scheduling submitted? NA YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? N/A