The Chemistry Review for NDA 22-307

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA was reviewed as part of the Pharmaceutical Quality Assessment System (PQAS) Pilot Program, and as amended, it may be approved from the CMC review perspective since all critical review issues related to approvability have been satisfactorily resolved. The cGMP status of manufacturing facilities is still pending with the Office of Compliance so a final recommendation cannot be given at this time.

The information provided in the NDA supports the approval of 5 and 10 mg tablets, packaged in ——— bottles with desiccant (30 counts for 5 and 10 mg tablets, 7 counts for 5 mg tablets) or in unit dose ——— blisters (10 mg tablets only). An expiration dating period of — months, when stored at 25°C (USP Controlled Room Temperature) is supported by the stability data for the bottle configuration. 10 mg tablets, stored in blisters will have an expiration dating period of 12 months. b(4)

Lilly should be informed in the action letter for this application that they should follow current postapproval regulations and guidances if they wish to perform analytical testing at facilities other than those listed in the NDA.

Regarding the timing of the reformulation of the product, i.e. pre- or post-approval, the CMC review team's preference as stated in Review #1 dated May 14, 2008 was to have this performed prior to NDA approval. However, there have been several developments since then which have convinced us that marketing the current formulation with a post-approval commitment to reformulate would be acceptable:

- There have been extensive discussions with the Clinical Pharmacology and Clinical reviewers of this NDA as well as with the Cross Discipline Team Leader, Division Director and Office Director concerning the clinical implications of form conversion and the consensus is that, although suboptimal from a quality viewpoint, the presence of a mixture of salt and free base in Effient appears not to have any bearing on safety and efficacy.
- The Clinical Pharmacology reviewer has noted in her review dated, May 23, 2008, that the 30% difference in Cmax for the active metabolite in patients on PPI treated with high conversion tablets did not change the PD response and consequently may not have clinical significance.
- Lilly has proposed that ——— and this is acceptable to the Clinical Pharmacology Team Leader. b(4)

- In addition to [redacted] with the new formulation, Lilly has agreed to use it and the current formulation in a large clinical trial, TRILOGY, thereby allowing a direct comparison of the two products in patients. b(4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following commitments have been proposed by Lilly and are acceptable:

1) To develop a discriminating dissolution method for the current formulation by December 2008.
2) To reformulate the product [redacted] a supplement to the NDA no later than [redacted]

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1) Drug Substance

Prasugrel hydrochloride is a white to practically white solid [redacted]. It is a prodrug which is converted in vivo to an active metabolite. It has

b(4)

4 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

B. Description of How the Drug Product is Intended to be Used

Prasugrel tablets are intended to be used for reduction of atherothrombotic events and reduction of stent thrombosis in acute coronary syndrome (ACS). It is intended to be given as a 60mg loading dose followed by a 5mg or 10mg maintenance dose.

C. Basis for Approvability or Not-Approval Recommendation

b(4)

Upon evaluation of the information submitted in the amendment to the NDA dated April 30, 2008 and further discussions with team members from Clinical Pharmacology and Clinical divisions, it was determined that allowance of [redacted] in the finished product would result in finished tablets that are inelegant from a quality view

point, however this would have little implication on safety and efficacy. Thus the CMC team recommends an approval action. This decision was strengthened by the fact that the sponsor has agreed to reformulate the product by [redacted], and use the new formulation and the current formulation in a large clinical trial, TRILOGY, thereby allowing a direct comparison of the two products in patients. b(4)

It was indicated in review #1 that a limit of NMT [redacted] free base in the finished tablet would pose a labeling challenge as it is an unknown mixture of free base and salt. This hurdle was circumvented by including a sentence in the Description section of the package insert that though the tablet is formulated using prasugrel hydrochloride, a partial conversion from HCl salt to free base could occur during manufacturing and storage.

The only issue currently pending resolution is an overall recommendation from the Office of Compliance regarding the cGMP status of manufacturing facilities.

III. Administrative

A. Reviewer's Signature electronically signed in DFS

Sharmista Chatterjee, Ph.D.
Zhengfang Ge, Ph.D.
Kasturi Srinivasachar, Ph.D.

B. Endorsement Block electronically signed in DFS

Blair Fraser, Ph.D.

C. CC Block see DFS

17 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Zhengfang Ge
8/28/2008 01:10:02 PM
CHEMIST

Sharmista Chatterjee
8/28/2008 01:21:42 PM
CHEMIST

Kasturi Srinivasachar
8/29/2008 10:20:42 AM
CHEMIST

Blair Fraser
8/29/2008 02:22:32 PM
CHEMIST

NDA 22-307

Effient (prasugrel) Tablets
5 mg and 10 mg

Eli Lilly

Sharmista Chatterjee, Ph.D.
Zhengfang Ge, Ph.D.
Kasturi Srinivasachar, Ph.D.

Office of New Drug Quality Assessment
for
Division of Cardiovascular and Renal products

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 12

C. Basis for Approvability or Not-Approval Recommendation 13

III. Administrative 13

A. Reviewer's Signature electronically signed in DFS 13

B. Endorsement Block electronically signed in DFS 13

C. CC Block see DFS 13

Chemistry Assessment 14

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 14

S DRUG SUBSTANCE 14

P DRUG PRODUCT [Prasugel Hydrochloride, 5mg and 10mg Tablets] 83

A APPENDICES 212

R REGIONAL INFORMATION 212

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 213

A. Labeling & Package Insert 213

B. Environmental Assessment Or Claim Of Categorical Exclusion 216

III. List Of Deficiencies To Be Communicated 217

Chemistry Review Data Sheet

1. NDA 22-307

2. REVIEW # 1

3. REVIEW DATE: May 7, 2008

4. REVIEWERS: Sharmista Chatterjee, Zhengfang Ge, Kasturi Srinivasachar

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	Dec. 26, 2007
Amendment # 27	April 24, 2008
Amendment #32	April 30, 2008

7. NAME & ADDRESS OF APPLICANT:

Name: Eli Lilly and Company

Address: Lilly Corporate Center, Indianapolis, IN 46285

Representative: Cheryl Beal Anderson, PharmD, RAC

Telephone: 317-6519826

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Effient
b) Non-Proprietary Name (USAN): Prasugrel Hydrochloride
c) Code Name/#: LY640315, CS747
d) Chem. Type/Submission Priority:

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Inhibitor of platelet aggregation

11. DOSAGE FORM: Film Coated Tablets

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

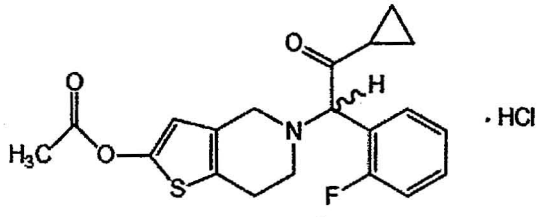
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:
(±)-2-[2-Acetyloxy-6,7-dihydrothieno[3,2-*c*]pyridin-5(*4H*)-yl]-1-cyclopropyl-2-(2-fluorophenyl)ethanone hydrochloride

Molecular Formula: $C_{20}H_{20}FNO_3S \cdot HCl$

Molecular Weight: 409.90

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
⌐					N/A		Components meet corresponding CFR codes. No need for individual review based on ONDQA policy
				⌟	Adequate	9-Jan-2007 By G. Lunn for NDA 21-971	

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,449	Clinical Development

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Low, medium and high conversion (salt to free base) tablets bioinequivalent in patients on PPI		P. Marroum
LNC	N/A		
Methods Validation	Post Approval		
DMETS	Pending		
EA	Categorical Exclusion Acceptable		
Microbiology	N/A		

The Chemistry Review for NDA 22-307

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA was reviewed as part of the Pharmaceutical Quality Assessment System (PQAS) Pilot Program, and as amended, it is APPROVABLE from the CMC perspective. The CMC review team conveyed its concerns regarding the quality of the to-be marketed product to Lilly in the Discipline Review letter dated April 9, 2008. Lilly has acknowledged that its current formulation [redacted] The CMC review team concurs with the general strategy of reformulation but recommends this be performed prior to NDA approval so that a highly variable drug product of questionable quality is not marketed. This is, however, not a final recommendation since Lilly has submitted additional information regarding the [redacted] which needs to be evaluated by the clinical pharmacology reviewer. They have also proposed to use the new formulation in the latter half of the clinical trial TABY and the merits of this approach have not yet been discussed from an interdisciplinary perspective. b(4)

Lilly's response to a question in the Discipline Review letter concerning the genotoxic potential of a number of degradation products is currently being evaluated by the pharm./tox. reviewer.

Inspection of manufacturing facilities is not complete at this time and an overall recommendation from the Office of Compliance is pending.

The basis for the APPROVABLE recommendation is discussed in greater detail in Section II C, below.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1) Drug Substance

Prasugrel hydrochloride is a white [redacted] solid [redacted] It is a prodrug which is converted in vivo to an active metabolite. It has b(4)

4 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

B. Description of How the Drug Product is Intended to be Used

Prasugrel tablets are intended to be used for reduction of atherothrombotic events and reduction of stent thrombosis in acute coronary syndrome (ACS). It is intended to be given as a 60mg loading dose followed by a 5mg or 10mg maintenance dose.

C. Basis for Approvability or Not-Approval Recommendation

On the basis of information provided in this NDA and in the amendment dated April 30, 2008, the CMC team recommends an approvable action, due to the perceived variability in end product quality. Our primary concern is the observed conversion of the prasugrel salt to free base. The rationale for our decision is follows:

(a) A review by the agency's clinical pharmacology reviewer of the data from the clinical study TACS, where three levels of converted tablets (5, 58 and 70%) were administered to patients with PPI, concluded that none of the conversion levels were bioequivalent to each other. In addition, the difference in plasma levels translated into differences in maximum platelet aggregation that could be clinically significant.

(b) The proposed revised specification of NMT ——free base over the shelf life of the product would still pose a wide variability in the quality of tablets. Furthermore, it would be a challenge to label the product accurately since it is an unknown mixture of free base and salt. b(4)

Other issues currently pending resolution are:
(i) An overall recommendation from the Office of Compliance regarding the cGMP status of manufacturing facilities.
(ii) Concurrence from the pharm./tox. reviewer on Lilly's QSAR approach to the evaluation of the genotoxic potential of a number of degradation products.

III. Administrative

A. Reviewer's Signature electronically signed in DFS

Sharmista Chatterjee, Ph.D.
Zhengfang Ge, Ph.D.
Kasturi Srinivasachar, Ph.D.

B. Endorsement Block electronically signed in DFS

Blair Fraser, Ph.D.

C. CC Block see DFS

204 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Sharmista Chatterjee
5/14/2008 10:07:39 AM
CHEMIST

Zhengfang Ge
5/14/2008 10:09:29 AM
CHEMIST

Kasturi Srinivasachar
5/14/2008 10:13:28 AM
CHEMIST

Blair Fraser
5/14/2008 05:04:35 PM
CHEMIST