CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-307

CHEMISTRY REVIEW(S)

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

Chemistry Review Data Sheet

1. NDA 22-307

2. REVIEW # 3

3. REVIEW DATE: June 12, 2009

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Review #1	May 7, 2008
Review #2	Aug 28, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment BC	Dec 18, 2008
Amendment BC	March 5, 2009
Amendment BL	March 11, 2009
Amendment BC	April 24, 2009
Amendment BL	June 10, 2009

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

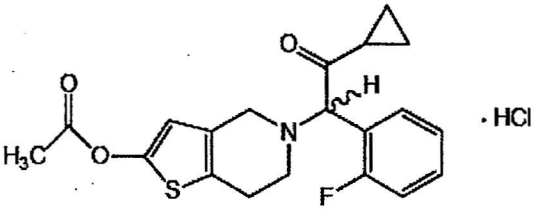
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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:
See Review #1

B. Other Documents:
See Review #1 and #2

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	06-Sep-2008	Office of Compliance
Pharm/Tox	N/A		
Biopharm	Low, medium and high conversion (salt to free base) tablets bioinequivalent in patients on PPI	May 23, 2008	P. Marroum and E. Mishina
LNC	N/A		
Methods Validation	See review in section P.5.3.	April 9, 2009	Changning Guo, DPA/OPS/CDER, St. Louis
DMETS	See Section III/A	May 29, 2008	Tara Turner
EA	Categorical Exclusion		

Chemistry Review Data Sheet

	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 may be approved from the CMC review perspective since all critical review issues related to approvability have been satisfactorily resolved.

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 18 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 post approval regulations and guidances if they wish to perform analytical testing at facilities other than those listed in the NDA.

As noted in review #2, the CMC review team has concluded that marketing the current formulation with a post-approval commitment to reformulate would be acceptable. Recent data submitted by Lilly have established that the extent and ———

b(4)

There was extensive discussion among Senior Management Staff whether reformulation should be a Postmarketing Requirement (PMR) or Postmarketing Commitment (PMC) under FDAAA provisions and a consensus has emerged that a PMC to reformulate and conduct supporting ——— would be more appropriate. 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 reformulate the product with ——— and submit a supplement to the NDA no later than ——— b(4)

II. Summary of Chemistry Assessments

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

1) Drug Substance

See reviews #1 and 2.

2) Drug Product

For background information refer to reviews # 1 and 2. The following section includes updated information about: dissolution method, updated stability data, revised acceptance criteria for ——— for detection of ——— b(4)

The sponsor had made a commitment in the amendment # 32 dated 30 April 2008, that they would submit an updated dissolution method that is more discriminatory of formulation and manufacturing process changes. In the amendment #74, dated December 18, 2008, the sponsor submitted information for a revised dissolution method that uses USP Apparatus II with 900 mL of pH 4.0, 50 mM acetate medium (USP) and a paddle speed of 75 rpm. This method would replace the original method for release of batches as well as for ongoing stability studies. The acceptance criteria proposed for this method was Q — % at 60 minutes. Upon evaluation, the discriminatory power of the method was found to be adequate, however the acceptance criteria was found to be too liberal, considering that the updated data provided for the stability and validation batches showed — % release in 30 minutes. The sponsor was thus recommended to revise the acceptance criteria as Q — % at 30 minutes, to allow better discriminatory power to distinguish between low — and medium — amount of form conversion. In an amendment dated April 24, 2009, the sponsor indicated their acceptance of agency's recommended acceptance criteria for dissolution. b(4)

The applicant provided updated stability data that included form conversion data, in an email dated 19-Feb-2009 in response to Agency's request for the updated stability data for — batches packaged in blisters. These batches were all manufactured with improved drug product process control to ——— For these

b(4)

B. Description of How the Drug Product is Intended to be Used
See review #1.

C. Basis for Approvability or Not-Approval Recommendation

In the latest amendment to the NDA dated April 24, 2009, the sponsor revised drug product specification, based on the Agency's request, to NMT — , of form conversion, and also revised dissolution specification to Q= — ; at 30 min with a pH 4 dissolution medium. The revised specification would better control the quality of the drug

products than previously proposed specification. On the basis of updated stability data, the team recommends an expiration of 18 months for 5mg and 10mg strengths packaged in bottles, and 12 months of expiration for 10mg strength packaged in blisters. Overall, the CMC team recommends an approval action. This decision was strengthened by the fact that the sponsor has agreed to reformulate the product by — b(4)
———————————————————, 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.

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

Christine Moore, Ph.D.

C. CC Block see DFS

67 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
6/17/2009 02:23:48 PM
CHEMIST

Zhengfang Ge
6/17/2009 02:28:24 PM
CHEMIST

Kasturi Srinivasachar
6/17/2009 02:58:53 PM
CHEMIST

Christine Moore
6/19/2009 01:56:31 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

Chemistry Review Data Sheet

1. NDA 22-307

2. REVIEW # 2

3. REVIEW DATE: Aug 28, 2008

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Review #1	May 7, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	June 5, 2008
Amendment	June 16, 2008
Amendment	Aug 18, 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

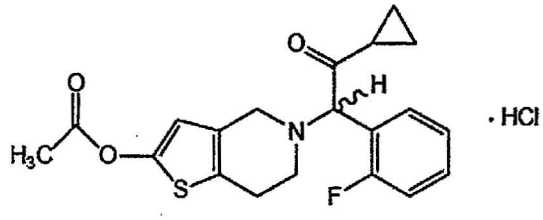
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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:
See Review #1

B. Other Documents:
See Review #1

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	May 23, 2008	P. Marroum and E. Mishina
LNC	N/A		
Methods Validation	Post Approval		
DMETS	See Section III/A	May 29, 2008	Tara Turner
EA	Categorical Exclusion Acceptable		

Microbiology	N/A		