Effient™
(prasugrel)
Tablets

NDA 22-307

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Indication: Reduction of atherothrombotic events and the reduction of stent thrombosis in acute coronary syndromes

Presentation: Film-coated, elongated hexagonal, immediate release, debossed tablet of either 5 mg (yellow) strength, supplied in 7 and 30 count bottles, or 10 mg (beige) strength, supplied in 30 count bottles; additionally, 10 mg strength supplied in unit dose blisters.

EER Status: Pending
Consults: BioPharm
Acceptable 23May2008
EA – Categorical exclusion granted under 21 CFR §25.31(b)
Methods Validation – Revalidation by Agency to be requested.

Original Submission: 26-DEC-2007

Post-Approval Agreements:

The applicant agreed to reformulate the drug product with: _________ and submit a supplement to the approved application no later than _________.

The applicant agreed to develop a discriminating dissolution method for the current formulation by December, 2008.

Background for CMC Section of Application:

The CMC portion of this NDA was submitted on December 26, 2007, under the Pharmaceutical Quality Assessment System (PQAS) Pilot Program, to explore science- and risk-based approaches to assuring product quality. A comprehensive Quality Overall Summary (Module 2) and an expanded pharmaceutical development section (P.2 in Module 3) were submitted. Several quality-by-design (QbD) elements were presented for product design and process understanding of the drug product.
Drug Substance:

The drug substance, prasugrel hydrochloride, is an adenosine diphosphate (ADP) receptor antagonist and a potent inhibitor of platelet activation and aggregation; it is a pro-drug that converts \textit{in vivo} into the active metabolite. It is a small, synthetic, new molecular entity (NME) with an empirical formula of $\text{C}_{20}\text{H}_{20}\text{FNO}_{3}\text{S}\cdot \text{HCl}$ and a molecular weight of 409.90. Known chemically as ($\pm$)-2-[2-Acetyloxy-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl]-1-cyclopropyl-2-(2-fluorophenyl) ethanone hydrochloride, it is a white solid that melts at $\text{(b(4))}$. The drug substance contains one chiral center and has been developed as a racemate. Prasugrel hydrochloride displays a
Conclusion: Drug substance is acceptable.

Drug Product:

The drug product is an immediate release tablet of 5 mg or 10 mg strength of prasugrel, with the following description:

- 5 mg, yellow, elongated hexagonal, film-coated, not scored tablet, debossed with “5 MG” on one side and “4760” on the other side, supplied in bottles of 30 count.

- 10 mg, beige, elongated hexagonal, film-coated, not scored tablet, debossed with “10 MG” on one side and “4759” on the other side, supplied in bottles of 30 count and unit-dose blisters.

- The composition of the 5 mg strength tablet is prasugrel hydrochloride (5.49 mg), mannitol USP (---), hypromellose USP (---), croscarmellose sodium NF (--- mg), microcrystalline cellulose NF (---), and magnesium stearate NF (---) for a total core weight of (---) mg; yellow film coating (---) gives total tablet weight of (---) mg.
The composition of the 10 mg strength tablet is prasugrel hydrochloride (10.98 mg), mannitol USP, hypromellose USP, croscarmellose sodium NF mg), microcrystalline cellulose NF, magnesium stearate NF ( for a total core weight of mg. The colored film coating gives total tablet weight of mg.

The colored film coating contains lactose, hypromellose, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red.

Adequate stability data were provided to support the proposed expiration dating of:

- —months for the drug product at 5 mg and 10 mg strengths, stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), packaged at 7 or 30 count in the proposed —bottles with — desiccant sachet.
- 12 months for the drug product at 10 mg strength, stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), packaged in the proposed unit-dose blisters.

Conclusion: Drug product is acceptable.

Additional Items:

- All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.
• The applicant has adequately responded to all deficiencies noted in the 7-MAR-2008 information request letter and the 9-APR-2008 discipline review letter.

• The applicant proposed a protocol for post-approval.

• The applicant agreed to add at least \( b(4) \) of drug substance per year to the stability monitoring program following the approved drug substance stability protocol.

• The applicant agreed to continue the primary stability studies on the \( b(4) \) commercial scale lots of each strength to firmly establish the proposed shelf life.

• The applicant agreed to place the first \( b(4) \) commercial production of drug product on stability for each strength and package configuration following the approved stability protocol.

• The applicant agreed to place at least \( b(4) \) of the drug product per year on stability, for each strength and package configuration, following the approved stability protocol.

• The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product.

Overall Conclusion:

From a CMC perspective, the application is recommended for Approval, pending an acceptable recommendation from the Office of Compliance.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Blair Fraser
8/31/2008 12:31:46 PM
CHEMIST
Memorandum

To: NDA 22-307
From: Zhengfeng Ge, Kasturi Srinivasachar and Sharmista Chatterjee
Date: 9/18/2008
Re: EER pending status

As stated in the Division Directors memo dated August 31, 2008 and Review # 2 by Chemistry, Manufacturing and Controls reviewers that an overall recommendation from Office of Compliance (OC) regarding the cGMP status of manufacturing facility was pending. As of September 6, 2008 all sites listed in EES were found to be acceptable by OC. See report in the following page.
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<tr>
<th><strong>Application</strong>:</th>
<th>NDA 22307/000</th>
<th><strong>Sponsor</strong>:</th>
<th>ELI LILLY AND CO</th>
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<td><strong>Dosage Form</strong>:</td>
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<td><strong>Strength</strong>:</td>
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**FPA Contacts:**

- **S. GOLDIE**: Project Manager 301-796-2055
- **K. SRINIVASACHAR**: Review Chemist 301-796-1760
- **K. SRINIVASACHAR**: Team Leader 301-796-1760

**Establishment**: CFN: 1819470 FEI: 1819470
ELI LILLY AND COMPANY LILLY CORPORATE CENTER INDIANAPOLIS, IN 462850001

**Responsibilities**: FINISHED DOSAGE MANUFACTURER

| **Profile** | | **OAI Status**: | NONE |
|-------------|------------------|-------------|
| **Last Milestone**: | OC RECOMMENDATION | |
| **Milestone Date**: | 04-FEB-08 | |
| **Decision**: | ACCEPTABLE | |
| **Reason**: | DISTRICT RECOMMENDATION | |

**Establishment**: CFN: — FRI: —

**DMF No**: AADA:

**Responsibilities**: TCM

| **Profile** | | **OAI Status**: | NONE |
|-------------|------------------|-------------|
| **Last Milestone**: | OC RECOMMENDATION | |
| **Milestone Date**: | 09-JAN-08 | |
| **Decision**: | ACCEPTABLE | |
| **Reason**: | BASED ON PROFILE | |

**Establishment**: CFN: — FRI: —

**DMF No**: AADA:

**Responsibilities**: UBE INDUSTRIES LTD.
UBE CITY, YAMAGUCHI, JA

**DMF No**: AADA:

**Responsibilities**: b(4)
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/s/

Sharmista Chatterjee
9/18/2008 04:00:59 PM
CHEMIST

Zhengfang Ge
9/19/2008 09:31:33 AM
CHEMIST

Kasturi Srinivasachar
9/22/2008 03:57:20 PM
CHEMIST

Blair Fraser
9/23/2008 05:12:29 AM
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