**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

| | |
|---|---|
| Date: | January 21, 2009 |
| To: | Norman Stockbridge, M.D., Director<br>Division of Cardiovascular and Renal Products, HFD-110 |
| Through: | Kellie Taylor, Pharm.D., M.P.H., Team Leader<br>Denise Toyer, Pharm.D., Deputy Director<br>Carol Holquist, R.Ph., Director<br>Division of Medication Error Prevention and Analysis, HFD-420 |
| From: | Tara Turner, Pharm.D., Safety Evaluator<br>Division of Medication Error Prevention and Analysis, HFD-420 |
| Subject: | Label and Labeling Review |
| Drug Name(s): | Effient<br>(Prasugrel Hydrochloride) Tablets<br>5 mg and 10 mg |
| Application Type/Number: | NDA #: 22-307 |
| Applicant: | Eli Lilly and Company |
| OSE RCM #: | 2008-1456 |

# CONTENTS

## EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container label, carton and insert labeling are vulnerable to confusion that could lead to medication errors. Specifically, the concerns surround the differentiation between the two strengths, as well as the instructions for proper dosage and administration of the drug product. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

## 1 BACKGROUND

### 1.1 INTRODUCTION

This review was written in response to a request from the Division of Cardiovascular and Renal Products (DCRP) to evaluate the labels and labeling of Effient for the potential to contribute to medication errors. The Applicant submitted revised container labels, carton and insert labeling for our review. Furthermore, we note that the proposed proprietary name was found acceptable in OSE Review # 2007-387 dated March 23, 2007 and OSE Review # 2008-79 dated May 29, 2008, and the Risk Evaluation and Mitigation Strategy (REMS) for this product was assessed in OSE Review # 2008-227, dated October 7, 2008.

### 1.2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis previously reviewed the container labels, carton and insert labeling for Effient and provided recommendations for improvement in OSE Review # 2008-79, dated May 29, 2008. The Division forwarded our comments from that review to the Applicant via e-mail dated June 6, 2008. In response, the Applicant submitted revised container labels and carton labeling on June 11 and June 25, 2008. Additionally, the Division provided us with the current version of the draft insert labeling, dated December 3, 2008.

### 1.3 PRODUCT INFORMATION

Effient (prasugrel hydrochloride) is an orally bioavailable prodrug metabolized to an active adenosine diphosphate (ADP) receptor antagonist, which is a potent inhibitor of platelet activation and aggregation. It is proposed for the reduction of cardiovascular events in acute coronary syndrome (ACS) patients 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) when managed with primary or delayed PCI

Effient will be available as 5 mg and 10 mg film-coated oral tablets. The 5 mg tablets will be supplied in bottles of 7 and 30. The 10 mg tablets will be supplied in bottles of 30 and blisters of 90. Treatment should be initiated with a single 60 mg loading dose and then continued at a 10 mg once daily dose. Patients taking Effient should also take aspirin (75 mg to 325 mg) daily.

## 2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to

inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

### 2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because DMEPA staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

The Division provided us with the version of the insert labeling as of December 3, 2008, which is actively being worked on by the review team (no image).

For this product the Applicant submitted on June 11, 2008 and June 25, 2008 the following revised labels and labeling for our review (see Appendices A through E for images):

- Blister Card: 10 mg (6 tablets)
- Blister Carton: 10 mg (90 tablets)
- Container: 10 mg (30 tablets)
- Container: 5 mg (30 tablets)
- Container: 5 mg (7 tablets)

Additionally, we reviewed the comments provided in OSE review # 2008-79 to identify outstanding areas of concern.

## 3 RESULTS

### 3.1 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels, carton and insert labeling identified areas of vulnerability that could lead to medication error, specifically with respect to differentiation between the two strengths, as well as the instructions for proper dosage and administration.

---

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

### *3.1.1 Container Labels and Carton Labeling*

The 5 mg strength is presented in light orange font.

The 10 mg strength is presented in the same green color as the proprietary name.

The labels and labeling for both strengths, with the exception of the blister card, contain a picture of a tablet with the strength, 5 mg or 10 mg, printed inside.

The container labels for both strengths have a purple band at the bottom.

### *3.1.2 Insert Labeling*

The proposed REMS for this product states that the loading dose should be given to the patient in a hospital setting. However, this information is not stated in the current version of the insert labeling.

The proposed REMS describes a recommended dose adjustment to 5 mg daily for patients <60 kg or for patients ≥ 75 years of age. However, this information is not stated in the current version of the insert labeling.

## 4 DISCUSSION

Our Label and Labeling Risk Assessment found the similarity of the container labels for both strengths introduces vulnerability that could lead to medication errors involving selection of the wrong strength. Additionally, we are concerned that the insert labeling does not contain dosing information that is included in the REMS.

### 4.1 INSUFFICIENT DIFFERENTIATION OF PRODUCT STRENGTHS

We reiterate our concerns regarding the lack of differentiation of the two strengths. The container labels for the two strengths look similar in appearance. This similarity is attributed to several factors: the use of the same green color for the presentation of the proprietary name and the 10 mg strength, the use of a purple band across the bottom of the container labels, and the use of drawings of the tablets, both of which appear in yellow color. Presenting the 10 mg strength in a color that is different from that of the proprietary name will result in a unique appearance for that strength and will distinguish it from the 5 mg strength. Further, the tablet drawings enhance the similarity between the two strengths because they appear to have the same color and shape. For purposes of identification, it would be more helpful to use photographs of the actual products, which will more clearly illustrate the differences as opposed to the drawings.

Additionally, the applicant has attempted to differentiate the strengths by presenting the 5 mg strength in light orange font. However, this color is difficult to see because it has poor contrast with the white background. It does not serve as a strong differentiator in comparison to the overall visual similarity of the labels. The use of more sharply contrasting colors on the labels and labeling will improve readability and decrease the chance for selection error.

### 4.2 INSERT LABELING

As stated in our previous review, we are concerned about potential errors that may result from confusion about proper administration of the loading dose for Effient as post-marketing experience has shown that medication errors occur when patients are required to use multiple units to achieve the prescribed dose. For Effient, a patient would be required to take six of the 10 mg tablets to achieve the loading dose of 60 mg. However, we have learned from the proposed REMS for this product that the loading dose should be given under medical supervision in a hospital setting. Therefore, our concern is minimized. However, we note that this information regarding the administration of the loading dose in the hospital setting is not stated in the current version of the insert labeling.

Similarly, the proposed REMS provides a recommended dosage adjustment in patients <60 kg or ≥ 75 years of age. However, this recommendation is not stated in the current version of the insert labeling.

We note that issues regarding the dosing of this product are currently under deliberation and may not have been resolved as of the date of this review. However, once this information is finalized, the insert labeling should be consistent with the REMS to avert any dosing confusion.

# 5 CONCLUSIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, the concerns surround the differentiation between the two strengths, as well as the instructions for proper dosage and administration of the drug product. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

# 6 RECOMMENDATIONS

## 6.1 COMMENTS TO THE DIVISION

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, Project Manager, at 301-796-1332.

### *A. Insert Labeling*

1. The Dosage and Administration (Section 2) and REMS have inconsistent dosing recommendations regarding the loading dose and administration in the hospital setting. Please revise once the dosing information is finalized.
2. The Dosage and Administration (Section 2) and REMS are inconsistent regarding the recommendations provided for dosage reduction in patients < 60 kg or ≥ 75 years of age. Please revise once the information is finalized.

## 6.2 COMMENTS TO THE APPLICANT

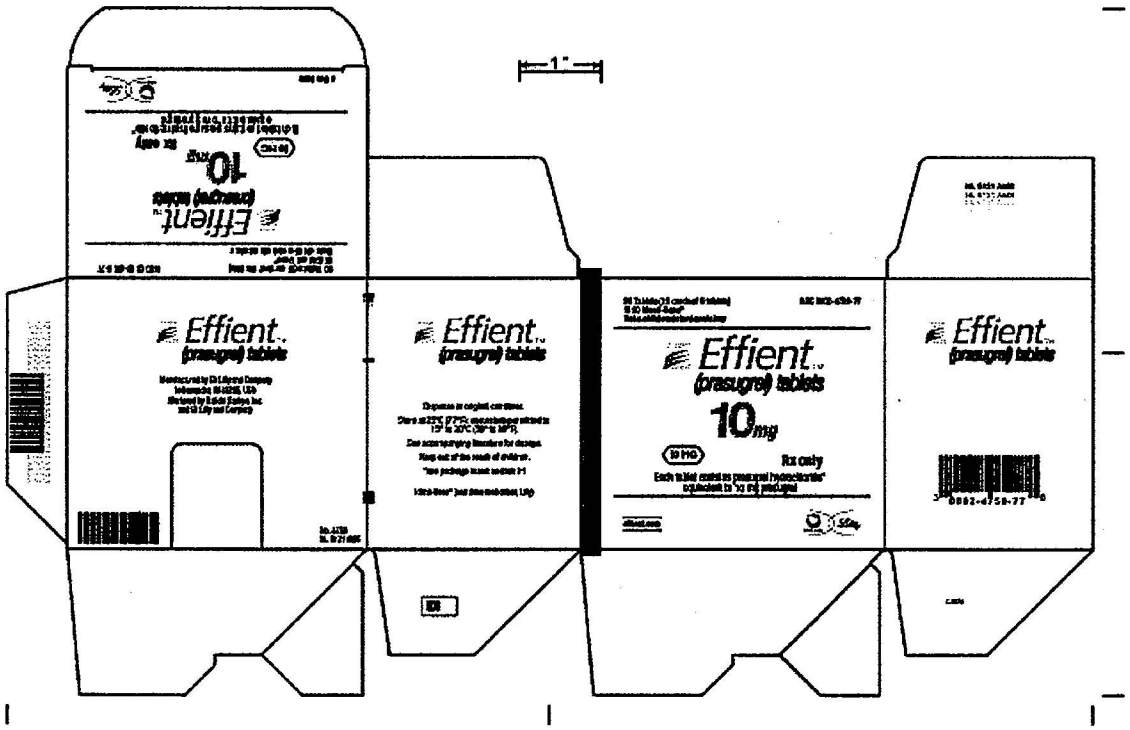
### *A. Container Labels (30's) and Carton Labeling*

1. Change the font color of the 10 mg strength to a color other than green since green is used to display the proprietary name. This will help to further differentiate the two product strengths.
2. Improve the contrast of the font color for the 5 mg strength. This could be achieved by outlining, boxing, use of an alternate color, or some other means.
3. Delete the purple band from the bottom of the container labels.
4. Consider using photographs of the actual tablets instead of graphic drawings of the tablets or deleting the images.
5. Insert a space between the number 10 and the unit designation "mg" on the 10 mg carton labeling.

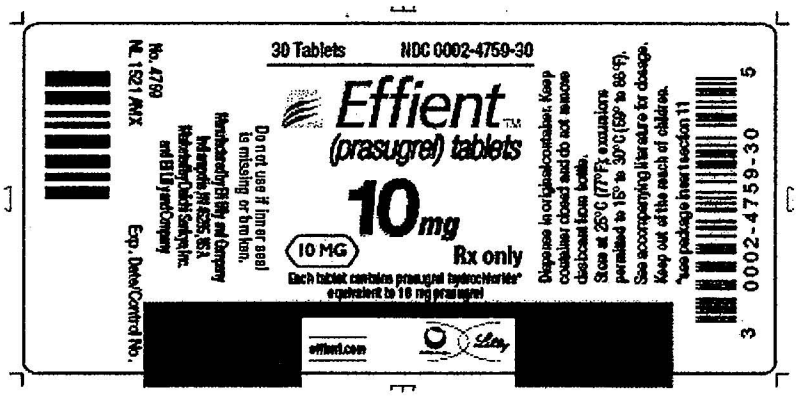
## APPENDICES

**<u>Appendix A:</u> Blister Card: 10 mg (6 tablets)**

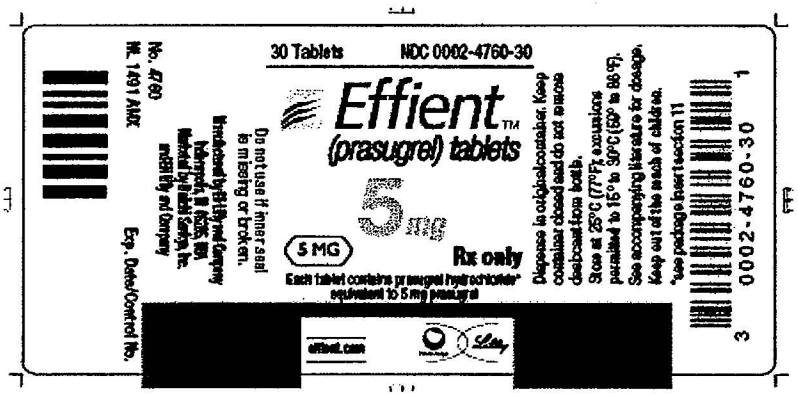
**Appendix B:** **Blister Carton: 10 mg (90 tablets)**



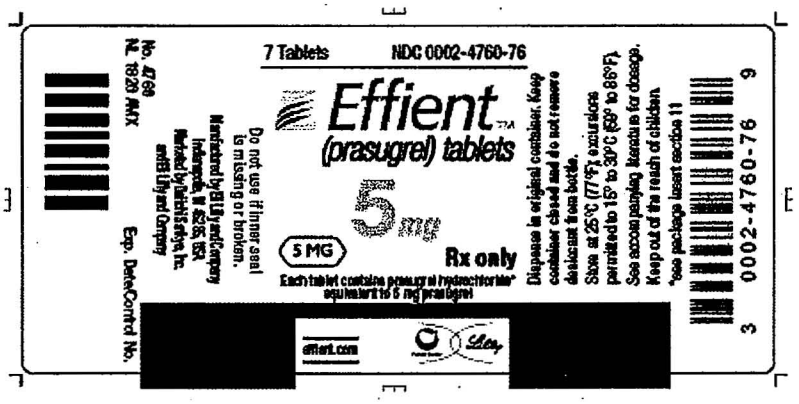
**Appendix C:** **Container: 10 mg (30 tablets)**




**Appendix D:** **Container: 5 mg (30 tablets)**



**Appendix E:** **Container: 5 mg (7 tablets)**



---

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

---

/s/
---
Kellie Taylor
1/21/2009 03:32:14 PM
DRUG SAFETY OFFICE REVIEWER
signing also for T. Turner

Denise Toyer
1/22/2009 06:27:14 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/22/2009 09:05:27 AM
DRUG SAFETY OFFICE REVIEWER