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

Date:	March 13, 2009
To:	Norman Stockbridge, M.D., Director Division of Cardiovascular and Renal Products (DCRP)
Through:	Kellie Taylor, Pharm.D., M.P.H., Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Tara Turner, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name(s):	Effient (Prasugrel Hydrochloride) Tablets 5 mg and 10 mg
Application Type/Number:	NDA # 22-307
Applicant:	Eli Lilly and Company
OSE RCM #:	2008-1456

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Effient, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Effient, for this product.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change.

In addition, the proposed name must be re-evaluated 90 days before approval of the NDA, even if the proposed product characteristics as stated in this review are not altered.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Cardiovascular and Renal Products (DCRP) for re-assessment of the proposed proprietary name, Effient, regarding potential name confusion with other proprietary or established drug names in the usual practice settings. The labels and labeling for this product were reviewed in OSE Review # 2008-79 dated May 29, 2008 and OSE Review # 2008-1456 dated January 22, 2009.

1.2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis previously reviewed and had no objection to the proposed proprietary name, Effient, in OSE Review # 2007-387 dated March 23, 2007 and OSE Review # 2008-79 dated May 29, 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 the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment (See 2.1 Proprietary Name Risk Assessment). The primary objective for the assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA 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 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center.

For the proposed proprietary name, DMEPA staff searched a standard set of databases and information sources to identify names with orthographic and phonetic similarity (See 2.1.1 for details) and held a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (See 2.1.1.2). DMEPA staff also conducts internal CDER prescription analysis studies. When provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment. However, since this name was previously evaluated, CDER prescription analysis studies were not conducted upon re-review of Effient.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (See 2.1.2 for details). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to, established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name

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

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

2.1.1 Search Criteria

The DMEPA staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'E' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[4,5]

To identify drug names that may look similar to Effient, the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (four: one capital letter 'E', two lower case 'f's, and one lower case 't'), downstrokes (two, lower case 'f's), cross-strokes (four, capital 'E', lower case 't', and two lower case 'f's) and dotted letters (one, lower case 'i'). Additionally, several letters in Effient may be vulnerable to ambiguity when scripted, including the lower case letter 'f' may appear as a lower case 't' 'b', or 'p'; lower case 'e' may appear as a lower case 'i', 'l', 'u', or 'o'; lower case 'i' may appear as a lower case 'e' or 'r'; lower case 'n' may appear as a lower case 'u', 'v', 'h', 's', 'r', or 'x'; lower case 't' may appear as a lower case 'r'; lower case letters 'ie' may appear as lower case 'u'. As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Effient.

When searching to identify potential names that may sound similar to Effient, the DMEPA staff searches for names with similar number of syllables (3), stresses (EFF-i-ent or ef-FI-ent), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary such as the letter 'E' may be interpreted as 'I' or 'A'; the letter 'f' may be interpreted as 'v' or 'ph'; or the letter 't' may be interpreted as 'd'. The Applicant's intended pronunciation of the proprietary name is presented as (EF'-fee-ent) in the Medication Guide. However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

The DMEPA staff also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the following information was provided about the proposed product to the medication error staff: proposed proprietary name (Effient), established name (prasugrel hydrochloride), proposed indication of use (reduction of cardiovascular events in ACS patients with unstable angina or NSTEMI who are managed with PCI and patients with STEMI who are managed with primary or delayed PCI), strength (5 mg and 10 mg), dose (loading dose of 60 mg; maintenance dose of 10 mg once daily), frequency of administration (daily), route (oral), and dosage form (film-coated tablet). Appendix A provides a more detailed listing of the product characteristics the medication error staff generally takes into consideration.

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

[4] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[5] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

Lastly, the DMEPA staff also considers the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, these broader safety implications of the name are considered and evaluated throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name was provided to the DMEPA staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the medication error staff used a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff reviewed the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators were then pooled and presented to the CDER Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by DMEPA to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Error Prevention and Analysis (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed.

The pooled results of the DMEPA staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 Comments from the Division of Cardiovascular and Renal Products

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. Any comments or concerns are addressed in the safety evaluator's assessment.

The regulatory division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The regulatory division is requested to concur /not concur with DMEPA's final decision.

2.1.3 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1, the Safety Evaluator Risk Assessment applies his/her individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it

might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name as a result of the name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking:

> ***"Is the name Effient convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?"***

An affirmative answer indicates a failure mode and represents a potential for Effient to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, then the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies; for example, product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

DMEPA will object to the use of proposed proprietary name when one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a proprietary name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].

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[6] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN (United States Adopted Names) stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product is awarded approval first has the right to use the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these criteria are met, then DMEPA will not object to the use of the proprietary name. If any of these criteria are met, then DMEPA will object to the use of the proposed proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP), who have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval.

Furthermore, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and other post-approval efforts are low-leverage strategies that have proven to have limited effectiveness at alleviating medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Applicants have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (See Section4 for limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that

instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The searches yielded a total of twenty-five names as having some similarity to the name Effient. Six of these names were previously evaluated in OSE review # 2007-387 or # 2008-79. Since no product characteristics have been altered from the time when these reviews were completed, the original analyses are still valid and these names were eliminated from further analysis. The nineteen names not previously reviewed are: Effect, Effexor XR, ——— Effico, ——— Evamist, Effidiet, Effiprev, Effik, Alfenta, Effance, Effercet, Effiplen, Ethedent, Effiente, Aeffient, Effientt, Effientz, and EthiDent. b(4)

Ten of the nineteen names were thought to look like Effient (Effect, Effexor XR ——— Effico, ——— Evamist, Effidiet, Effiprev, Effik, and Alfenta). One name (EthiDent) was thought to sound like Effient. The remaining eight names (Effance, Effercet, Effiplen, Ethedent, Effiente, Aeffient, Effientt, and Effientz) were thought to look and sound similar to Effient.

Our searches also revealed that the proposed name, Effient, is trademarked in many foreign countries. All of these trademarks are registered to Eli Lilly and Company.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of December 11, 2008.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1.1. above) and noted no additional names thought to have orthographic or phonetic similarity to Effient. The Expert Panel indicated that the proposed name looks like the word "efficient". However, we note that this word is not typically used in prescribing and dispensing medications.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 Comments from the Division of Cardiovascular and Renal Products (DCRP)

DMEPA notified DCRP via e-mail that we had no objections to the proposed proprietary name, Effient, on February 19, 2009. Per e-mail correspondence from DCRP on February 26, 2009, they indicated that they concur with our assessment.

3.1.4 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator resulted in seven additional names which were thought to look or sound similar to Effient and represent a potential source of drug name confusion.

The names identified to have look-alike similarities are: Effee, Effetre, Effia, Efficin, Effontil, and Effacne. The name, Effienta, was identified to have look-alike and sound-alike similarities. Additionally, we note that attempts to identify the drug names Effance and EthiDent were unsuccessful. We assume that these names were misspelled during the search process (i.e. Effance for Effacne and EthiDent for Ethedent). Thus, we evaluated Effacne (identified by the primary safety evaluator) and Ethedent (already identified in section 3.1.1 above), respectively. As such, a total of twenty-four names were analyzed to