

If none of these conditions are met, then we will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; 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, World Health Organization, Joint Commission, and the Institute for Safe Medication Practices, 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, we contend 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 so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the 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 Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, we believe 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 limitations of the process).

If we object 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. We are likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for us to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 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, 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.⁷

Because Medication Error Prevention 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 FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

⁷ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

For this product the applicant submitted the following labels and insert labeling for our review on December 26, 2007 (see Appendices E, F, G for images):

- Bottle Container Labels: 5 mg (30 count) and 10 mg (30 count)

- Blister Carton Labeling: _____ 10 mg (90 count: 15 cards with 6 tablets each)
- Insert Labeling (no image)

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3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

We conducted a search of the internet, several standard published databases and information sources (see Section 7 References) for existing drug names which sound-alike or look-alike to Effient to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice settings. In total, twenty names were identified as having some similarity to the name Effient: Effer-K, Effexor, Seffin, Efferdent, Aggrenox, Efficort, Eskalith, Epipen, Aviane, Effical, Iberet, Iferex, Elimite, Epimide, Effluent, Efavirenz, Effervescent, Alupent, Effigel, and Efudex .

Ten of these names were previously evaluated. The ten names not previously reviewed are: Iberet, Iferex, Elimite, Epimide, Effluent, Efavirenz, Effervescent, Alupent, Effigel, and Efudex. Five of these names were thought to look like Effient (Iberet, Iferex, Elimite, Epimide, and Effluent). Two of the names (Efavirenz and Effervescent) were thought to sound like Effient. The remaining three names (Alupent, Effigel and Efudex) were thought to look and sound similar to Effient.

Additionally, the Division of Medication Error Prevention did not identify any USAN stems in the name, Effient, as of January 24, 2008.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by Medication Error Prevention staff (see section 3.1.1. above). The Expert Panel indicated that the proposed name Effient looks like "efficient" and may imply that the product is "efficient".

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 Safety Evaluator Risk Assessment

The primary safety evaluator, affording careful evaluation to drug names beginning with the letters 'E' and 'I', conducted independent searches which identified two additional names with similarity to Effient. Those names are Efidac and Epoetin and both were identified to have look-alike similarity with Effient. As such, a total of twelve names were analyzed to determine if the drug names could be confused with Effient and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Effient, and thus determined to present some risk for confusion. Failure Modes and Effects Analysis (FMEA) was then applied to determine if the proposed name, Effient, could potentially be confused with any of the twelve names and lead to medication error.

This analysis determined that the name similarity between Effient and the identified names was unlikely to result in medication errors for all twelve products. Two names (Effervescent and Alupent) were not considered further because they lack convincing orthographic and/or phonetic similarities with Effient. Effigel is a foreign drug product (diclofenac) which is available in Switzerland. Efidac is available in two formulations, both of which have been discontinued according to the Orange Book. There are no generic equivalents for these products (see Appendix B). Effluent is an adjective defined as “flowing out, emanating, or outgoing”. There is low likelihood of confusion with a drug name such as Effient, and thus Effluent will not be discussed further.

For one name (Iberet) it was determined that medication errors were unlikely because the product does not overlap in strength or dosage with Effient (see Appendix C).

The remaining six names (Iferet, Efavirenz, Elimite, Epimide, Efudex, and Epoetin) had some numerical overlap or similarities with Effient in dosage and strength, but analysis of the failure modes did not determine the effect of these similarities to result in medication errors in the usual practice setting (see Appendix D).

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels and carton labeling identified several potential sources of medication error, specifically with respect to clear communication of the product name and strength, and the similarity of the labels and labeling between the two strengths.

3.2.1 Container Labels and Carton Labeling

The established name is expressed as “prasugrel HCl” and the strength of each tablet as “equivalent to XX mg prasugrel”.

The container labels and carton labeling contain graphics which are prominent and distracting.

The established name is less than ½ the size of the proprietary name, which gives it less prominence.

The established name is presented in a thin font, which gives it less prominence than the proprietary name.

The dosage form “tablets” has less prominence than the rest of the established name.

The strength is not placed in an optimal location.

The 5 mg strength is presented in white font against a gray background, which is difficult to read.

The 10 mg strength is presented with the ‘mg’ intersecting part of the ‘10’, which is difficult to read.

The container label and carton labeling for both of the strengths are not well differentiated and they look similar in appearance.

The Lilly ID # is located too close to the product NDC #.

3.2.2 Insert Labeling

The proposed Risk Management Plan 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 insert labeling.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Effient, has some similarity to twelve other proprietary and established drug names, but the findings of the FMEA process indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

4.2 LABEL AND LABELING RISK ASSESSMENT

The results of the Label and Labeling Risk Assessment noted needed improvements with respect to the use of graphics and the location and prominence of important information such as the established name, dosage form, and strength.

Specifically, the container labels and carton labeling for the two strengths look similar in appearance due to use of the same trade dress and color scheme (green and gray) for both strengths. These colors do not serve as strong visual differentiators. Because these products will be stored side-by-side in the usual practice setting, this similarity may cause inadvertent product selection errors in strength. The product strength is also difficult to see because of the font colors used to express the strength (i.e., white font on gray background for 5 mg and white font on green for 10 mg). Additionally, with respect to the 10 mg strength, the unit of measure (mg) intersects the number '10'. All of these factors contribute to the similarity and decrease the distinction between the different strengths. The use of more sharply contrasting colors on the labels and the separation of the number '10' from the 'mg' will improve readability and decrease the chances for a selection error.

Another contributing factor to the label similarity is the use of pictures of tablets on the labels/labeling. The 5 mg tablet picture is yellow while the 10 mg is beige. However, these colors as they appear on the labels are extremely similar, despite the embossed strength on the tablets. This presentation may be a source of confusion as it does not play a role in distinguishing the two product strengths. In fact, the pictures of the tablets enhance the similarity between the two strengths.

Similarly, the unit dose labels for both strengths look-alike as well (black font on white background) and there is no distinction between the two strengths. The use of contrasting color or by other means (i.e., boxing the strength) will help to differentiate the two strengths.

In our analysis, we note that the graphics used on the labels/labeling (i.e., white/gray swooshes on 5 mg and light green/dark green swooshes on 10 mg) occupy the majority of the principal display panel, crowd the label, and detract attention away from other important information such as the established name and the product strength. Minimizing or deleting the use of such graphics will allow for increased label space that will allow for the enhancement of the visibility of the product information on the labels/labeling.

We also note in our analysis that the established name is expressed as "prasugrel HCl" and the strength of each tablet as equivalent to "XX mg prasugrel". This expression of strength, in terms of one form of the salt, is contrary to CDER and USP policy. In order to comply, the information should be presented as follows:

Effient
(prasugrel) tablets
XX mg

Additionally, the presentation of the established name, dosage form, and strength lacks prominence. The established name is in thin font, which decreases its prominence. The dosage form "tablets" should be presented with the same prominence as the rest of the established name. The product strength is presented at the bottom left of the principal display panel. Presenting the strength in this unusual manner increases the opportunity for confusion. Practitioners are accustomed to seeing the strength directly beneath the proprietary and established names when looking at a drug label/labeling. This preferred placement allows for easy identification by a healthcare practitioner and decreases confusion. Also, we note that the Lilly product ID # is presented directly beneath the NDC #. The manufacturer's product identification is not typically utilized in the medication use system and should therefore be removed from the labels and labeling to decrease clutter and to avoid the risk of confusion.

Finally, we are concerned about potential errors that may result from confusion about proper administration of the loading dose for Effient as postmarketing experience has shown that medication errors occur when patients are required to take different doses of the same strength. The loading dose for Effient would require six tablets of 10 mg to achieve the loading dose of 60 mg. However, we have learned from the proposed Risk Management Plan for this product that the loading dose should be given in a hospital setting. Therefore, our concern is minimized. Nonetheless, we note that this information is not stated in the package insert labeling. The product labeling should be consistent with the Risk Management Plan to avert any dosing confusion.

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Effient, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention does not object to the use of the proprietary name, Effient, for this product at this time. Additionally, DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval.

5.1 COMMENTS TO THE DIVISION

1. The Division of Medication Error Prevention does not object to the use of the proprietary name, Effient, for this product at this time. However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. If the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.
2. The Division of Medication Error Prevention believes the Label and Labeling risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

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 sponsor with regard to this review. If you have further questions or need clarifications, please contact Cheryl Wiseman, project manager, at 301-796-0567.

5.2 COMMENTS TO THE APPLICANT

5.2.1 *Proprietary Name*

1. The Division of Medication Error Prevention does not object to the use of the proprietary name, Effient, for this product at this time.
2. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review.

5.2.2 *Labels and Labeling*

A. Container Label and Carton Labeling

1. Revise the presentation of the established name and strength as follows, in accordance with CDER and USP policy:

Effient
(prasugrel) tablets
XX mg

Delete the equivalency statement located beneath the product strength (“Each tablet equivalent to XX mg prasugrel”).

2. Delete or decrease the prominence of the graphic displayed at the beginning of the proprietary name and the graphic on the principal display panel which surrounds the product strength.
3. Increase the prominence of the established name by increasing the font weight.
4. Increase the prominence of the dosage form “tablets” so that it is commensurate with the rest of the established name.
5. Relocate the product strength so that it appears directly beneath the established name of the product. Separate the number from the ‘mg’ so that the strength does not overlap with the unit of measure.
6. Increase the prominence of the 5 mg product strength by using a background color other than gray.
7. Use contrasting color or other means to differentiate between the two strengths.
8. Remove the tablet pictures.
9. Remove the Lilly ID #.

B. Insert Labeling

Include a statement that the loading dose should be administered in the hospital setting.

6 REFERENCES

1. *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. *Micromedex Integrated Index (<http://weblern/>)*

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

3. *Phonetic and Orthographic Computer Analysis (POCA)*

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the Division of Medication Error Prevention, FDA.

4. *Drug Facts and Comparisons, online version, St. Louis, MO (<http://weblern/>)*

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

5. *AMF Decision Support System [DSS]*

DSS is a government database used to track individual submissions and assignments in review divisions.

6. *Division of Medication Errors and Technical Support proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention from the Access database/tracking system.

7. *Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)*

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologics, discontinued drugs and "Chemical Type 6" approvals.

8. *Electronic online version of the FDA Orange Book (<http://www.fda.gov/cder/ob/default.htm>)*

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. **United States Patent and Trademark Office** <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

10. **Clinical Pharmacology Online** (<http://weblern/>)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. **Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com**

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. **Natural Medicines Comprehensive Databases** (<http://weblern/>)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. **Stat!Ref** (<http://weblern/>)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. **USAN Stems** (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

15. **Red Book Pharmacy's Fundamental Reference**

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. **Lexi-Comp** (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

17. **Medical Abbreviations Book**

Contains commonly used medical abbreviations and their definitions.