

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-320

PROPRIETARY NAME REVIEW(S)



**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: November 26, 2008

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Subject: Proprietary Name, Label and Labeling Review

Drug Name(s): Epiduo Gel
(Adapalene and Benzoyl Peroxide) Gel 0.1 %/2.5 %

Application Type/Number: NDA 22-320

Applicant: Galderma Laboratories, L.P.

OSE RCM #: 2008-1395

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Epiduo Gel, is not vulnerable to name confusion that could lead to medication errors. Therefore, the Division of Medication Error Prevention and Analysis has no objection to the use of the proposed proprietary name, Epiduo, 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 the name must be resubmitted for review. Additionally, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed labels and labeling are vulnerable to confusion that could lead to medication errors. Specifically, these areas of improvement include the large graphic that bisects the proprietary name on the container labels and carton labeling, statements regarding route of administration, the presentation of the established name and products strength and the Patient Counseling Information of the insert labeling. The Division of Medication Error Prevention and Analysis (DMEPA) believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Dermatology and Dental Products for assessment of the proposed proprietary name, Epiduo Gel, regarding potential name confusion with other proprietary or established names. Additionally, labels and labeling were submitted for evaluation for their potential to contribute to medication error.

1.2 PRODUCT INFORMATION

Epiduo Gel (adapalene and benzoyl peroxide) is a retinoid and antimicrobial combination product indicated for the topical treatment of acne vulgaris in patients 12 years of age and older. The usual dose is a pea-sized amount applied to each affected area once daily. The fingertips should be used for application of the gel, avoiding the eyes, lips and mucous membranes. Epiduo Gel will be available.

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2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the Division of Medication Error Prevention and Analysis staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Container Label, Carton, and Insert Labeling Risk Assessment). The primary focus for both 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

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Epiduo Gel, and the proprietary and established names of drug products existing in the marketplace and those pending IND, BLA, NDA, and ANDA products currently under review by CDER. Since we believe that practitioners may order this product as "Epiduo" (i.e. without including the "Gel" portion of the name), an identical name risk assessment was conducted for Epiduo.

For the proprietary name, Epiduo Gel, and the root name Epiduo, we search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). We also conduct internal FDA prescription analysis studies (see 2.1.3), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

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 detail 2.1.4). The overall risk assessment is based on the findings of a Failure Modes 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 look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. 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.³ Our Division uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in 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. As such, the Staff consider the product characteristics associated with the proposed drug throughout the risk assessment, since 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 drug name include, but are not limited to established name of the proposed product, the proposed indication, 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 confusion can occur at any point in the medication use process, we consider 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.⁴

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

³ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

⁴ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

2.1.1 Search Criteria

The Medication Error Staff consider 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.⁵⁶

To identify drug names that may look similar to Epiduo Gel/Epiduo, the Staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (9 letters), upstrokes (4, capital letters 'E' and 'G' and lowercase letters 'd' and 'l'), downstrokes (one, 'p'), cross-strokes (none), and dotted letters (one, 'i'). Additionally, several letters in Epiduo Gel/Epiduo may be vulnerable to ambiguity when scripted, including the letter 'E' may appear as 'F'; lower case 'p' appear as a lower case 'x' or the letters 'yn'; lower case 'i' may appear as lower case 'e', lower case 'd' may appear as the letters 'cl'; lower case 'u' may appear as 'n', 'r', 's', 'x', 'h' or 'y'; and lower case 'o' may appear as lower case 'a' or 's'; capital 'G' may appear as 'S'; lower case 'g' may appear as 'j' or 'q' or the number '8'; lower case 'e' may appear as 'i'; and lower case 'l' may appear as 'e' or 'b'. As such, the Staff also consider these alternate appearances when identifying drug names that may look similar to Epiduo Gel/Epiduo.

When searching to identify potential names that may sound similar to Epiduo Gel/Epiduo, the Medication Error Staff search for names with similar number of syllables (5 for Epiduo Gel, 4 for Epiduo), stresses (EPI-duo, epi-DUO or epidu-OH; Gel), and placement of vowel and consonant sounds. In addition, several letters in Epiduo may be subject to interpretation when spoken, including the letters "Epi" may be interpreted as 'Epe', or 'Epy'; the letter 'i' may be interpreted as 'y' or 'e'; and the letter 'o' may be interpreted as the letters 'oh' or 'ow'. As such, the staff also considers these alternate pronunciations when identifying drug names that may sound similar to Epiduo Gel/Epiduo. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider 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 Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Epiduo Gel), the established name (adapalene and benzoyl peroxide), proposed indication (acne vulgaris), strength (0.1%/2.5%), frequency of administration (once daily), route (topical) and dosage form of the product (gel). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration.

⁵ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁶ Kondrack, G and Dorrr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

Lastly, the Medication Error Staff also consider 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. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the Medication Error Staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name, Epiduo Gel, and the root name, Epiduo, were provided to DMEPA 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 Epiduo Gel/Epiduo using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 6. To complement the process, the Medication Error Staff use 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 Medication Error Staff review the United States Adopted Names (USAN) stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.2 CDER Expert Panel Discussion

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

The pooled results of the medication error 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.

2.1.3 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Epiduo Gel with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Epiduo handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to the medication error staff.

Figure 1. Epiduo Gel Study (conducted on October 7, 2008)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Outpatient Prescription:</u></p> <p>Epiduo # 1 Apply a pea-sized amount to the affected area(s) once daily.</p>	<p>Epiduo # 1 Apply a pea-sized amount to the affected area(s) once daily</p>
<p><u>Inpatient Medication Order:</u></p> <p>Epiduo Apply a pea-sized amt. to the affected area(s) once daily</p>	

2.1.4 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk 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.⁷ When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention and Analysis seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and 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 look- or sound-alike 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 a 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 Epiduo Gel/Epiduo convincing 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 Epiduo Gel/Epiduo to be

⁷ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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 and 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 ultimately not 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, such as 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.

The Division of Medication Error Prevention and Analysis will object to the use of proposed proprietary name when the 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 trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. We identify 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 stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. 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 another drug product.

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

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 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, The World Health Organization, The Joint Commission,

and The Institute For Safe Medication Practices, which 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, the Division of Medication Error Prevention and Analysis 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 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 Applicant, 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 Applicant'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. Our Division is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for review by our Division. 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 Applicant 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, 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.⁸

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.

⁸ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

For this product, the Applicant submitted on June 6, 2008 the following labels for our review (see Appendices H and I for images):

- 
- Retail Container Labels:   **b(4)**
- Carton Labeling: 
- Insert Labeling (no image)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

In total, 17 names were identified as having some similarity to the name Epiduo. Fifteen of the seventeen names were thought to look like Epiduo, which include: Epitol,  Epipen, Epicort, Epivir, Epidri, Epident,  Epiderm,   Epifil, Apidra, Equetro and Epulor. Two names ( and Epiduo) were thought to look and sound similar to Epiduo. **b(4)**

As of October 24, 2008, the proposed name, Epiduo Gel/Epiduo, did not contain a United States Adopted Name (USAN) stem.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by Medication Error Staff (see section 3.1.1. above), and no additional names were thought to have orthographic or phonetic similarity to Epiduo Gel/Epiduo.

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 FDA Prescription Analysis Studies

A total of 24 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About 88% of the participants (n=21) interpreted the name correctly as "Epiduo", with correct interpretation occurring more frequently in the outpatient written study. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator did not identify any additional names, thought to look and/or sound similar to Epiduo Gel/Epiduo and represent a potential source of drug name confusion. As such, a total of seventeen names were analyzed to determine if the drug names could be confused with Epiduo Gel/Epiduo 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 Epiduo, and thus determined to present some risk of confusion. Thus, Failure modes and effects analysis (FMEA) was then applied to determine if the proposed name, Epiduo Gel/Epiduo, could potentially be confused with any of the seventeen names and lead to medication errors. This analysis determined that the name similarity between Epiduo Gel/Epiduo and the identified names was unlikely to result in medication errors for all of the identified products for the reasons described in Appendices C through G.

3.2 LABEL AND LABELING RISK ASSESSMENT

Upon review of the container label, carton and insert labeling, the Division of Medication Error Prevention and Analysis notes the following:

3.2.1 General Comment

The product strength is embedded in the established name and the active ingredients are separated with either a “slash mark” or the word “and” [(adapalene 0.1%/ benzoyl peroxide 2.5%) or (adapalene 0.1% and benzoyl peroxide 2.5%)].

3.2.2 Container Labels and Carton Labeling (30 gram and 60 gram)

The proprietary name is difficult to read because it appears in two different colors and is bisected by a prominently displayed graphic.

The statement “For external use only” does not appear on the principal display panel.

3.2.3 Package Insert Labeling

The Dosage and Administration section of the Highlights of Prescribing Information does not contain the frequency of administration for the product.

There is no information in Section 17 (Patient Counseling Information) regarding exposure to sunlight and sunlamps or concomitant use of potentially irritating topical products while using Epiduo.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

We evaluated a total of 25 names for their potential similarity to Epiduo. Our FMEA found the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors in the usual clinical practice setting.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise once the product is commercially marketed. However, DMEPA believes that these limitations are sufficiently minimized by the use of an Expert Panel.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, the proprietary name must be re-reviewed if approval of the product is delayed beyond 90 days.

4.2 LABEL AND LABELING RISK ASSESSMENT

Our Label and Labeling Risk Assessment found several areas of needed improvement.

4.2.1 Presentation of the Proprietary Name

The Applicant presents the proprietary name in two different colors and uses graphic circles which bisect the presentation of the proprietary name on the container and carton labeling. These graphic circles affect the readability of the proprietary name. Additionally, the font colors used for the letters 'duo' are similar to the colors used in the graphic circles adding to the poor readability of this presentation. Moreover, using different colors highlights the "Epi" portion of the name. Epi is a common term used for epinephrine. Highlighting this prefix may inadvertently suggest the product contains epinephrine.

4.2.2 Established Name

We note that the product strength is embedded in the established name and the active ingredients are separated with either a "slash mark" or the word "and" (adapalene 0.1%/ benzoyl peroxide 2.5%) or (adapalene 0.1% and benzoyl peroxide 2.5%). The CMC review recommends that the established name be presented as follows:

(adapalene/benzoyl peroxide) gel
0.1%/2.5%

This presentation should be used throughout the labels and labeling.

4.2.3 Route of Administration

The route of administration statement "For external use only" is bolded and does not appear on the principal display panel. In its current location the statement can be easily overlooked. Addition of this important information to the principal display panel ensures adequate prominence of this statement.

4.2.4 Dosing

The frequency of application (once daily _____) should be included in the Dosage and Administration section of the Highlights of Prescribing Information as this is essential dosing information. This is in accordance with 21 CFR 201.57 (a)(7).

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4.2.5 Patient Counseling Information

There is information in the insert labeling regarding exposure to sunlight and sunlamps (Section 5.1, Warnings and Precautions) and the concomitant use of potentially irritating topical products (Section 7, Drug Interactions) which does not have corresponding patient information. Providing references to this information in the Patient Counseling Information (Section 17) would help to ensure the safe use of this product. This is in accordance with 21 CFR 201.57 (c)(18).

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Epiduo Gel, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Epiduo, 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. Additionally, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

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. We believe the risks identified can be addressed and mitigated prior to drug approval, and provide 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 the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

6.2 COMMENTS TO THE APPLICANT

A. Proprietary Name

DMEPA has no objections to the use of the proprietary name, Epiduo, 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, the medication error prevention staff rescinds this Risk Assessment finding, and the name must be resubmitted for review. Additionally, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

B. General Comments

1. Relocate the statement "For external use only" to appear on the principal display panel on the container labels and carton labeling.
2. Revise the presentation of the established name and strength on all the labels and labeling to read as follows:

(adapalene/benzoyl peroxide) gel
0.1%/2.5%

3. Use the same "color" for each portion of the proprietary name. The use of two colors highlights the letters "Epi". Epi is a common term for the active ingredient epinephrine. Highlighting this prefix may lead healthcare practitioners to think that the product contains epinephrine. The entire name should appear in the same color. Additionally, remove the graphic circles which bisect the proprietary name to improve the readability of the name.

C. Insert Labeling

1. Revise the Dosage and Administration section of the Highlights of Prescribing Information to include the frequency of administration for the product (i.e., once daily _____), to be in accordance with 21 CFR 201.57(a)(7).
2. Revise the Patient Counseling Information (Section 17) to include information regarding exposure to sunlight and sunlamps (Section 5.1, Warnings and Precautions) and the concomitant use of potentially irritating topical products (Section 7, Drug Interactions) while using Epiduo, to Be in accordance with 21 CFR 201.57(c)(18).

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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 manufacturers 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 post marketing 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://csi.micromedex.com>)*

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 and Analysis, FDA.

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

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 Prevention and Analysis proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis 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, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and 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. *U.S. Patent and Trademark Office (<http://www.uspto.gov>)*

Provides information regarding patent and trademarks.

10. *Clinical Pharmacology Online* (www.clinicalpharmacology-ip.com)

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 trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. *Natural Medicines Comprehensive Databases* (www.naturaldatabase.com)

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

13. *Stat!Ref* (www.statref.com)

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.lexi.com)

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

17. *Medical Abbreviations Book*

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. We also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has led to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the Division of Medication Error Prevention and Analysis will consider the Applicant’s intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, we also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes Cross-strokes	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		<p>Dotted letters</p> <p>Ambiguity introduced by scripting letters</p> <p>Overlapping product characteristics</p>	
Sound-alike	Phonetic similarity	<p>Identical prefix</p> <p>Identical infix</p> <p>Identical suffix</p> <p>Number of syllables</p> <p>Stresses</p> <p>Placement of vowel sounds</p> <p>Placement of consonant sounds</p> <p>Overlapping product characteristics</p>	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

FDA Prescription Study Responses

Outpatient Prescription	Inpatient Prescription	Phonetic Prescription
Epiduo	Epiduo	Epiduo
Epi-duo	Epidud	Epidus
EpiDuo	Epiduo	Epiduo
Epi Duo	Epidio or Epiduo	Epiduo
Epiduo		
Epiduo		
Epiduo		

Appendix C: Names lacking convincing look-alike and/or sound-alike similarities with Epiduo

Proprietary Name	Similarity to Epiduo
Epitol	Look
_____	Look
Epipen	Look
Epicort	Look
Epivir	Look
Epident	Look
_____	Look
Epiderm	Look
Epifil	Look
Equetro	Look
Epulor	Look

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Appendix D: Names of products marketed or trademarked in foreign countries

Proprietary Name	Similarity to Epiduo Gel	Country
Epiduo (adapalene/benzoyl peroxide) 0.1%/2.5%	Look and sound	France

Appendix E: Name is not a marketed drug product

Proprietary Name	Similarity to Mozobil	Product Information
_____	Look and sound	Medical procedure
_____	Look	Chemical substance
_____	Look	Chemical substance

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Appendix F: Product with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Epiduo Gel/Epiduo (Adapalene 0.1% and Benzoyl peroxide 2.5%)	N/A	0.1 % and 2.5%	Apply to acne affected area of skin once daily
Epidri (Epinephrine) Pellets Dental product	Look	1.9 mg	Dip in water just prior to application. (Indicated for drying up blood and saliva in preparation of a tooth.)

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Appendix G: Names that differ in usual dose.

Product Name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose
Epiduo/ Epiduo Gel (Adapalene 0.1% and Benzoyl peroxide 2.5%)	N/A	0.1 % and 2.5%	Apply to acne affected area of skin once daily
Apidra (Insulin Glulisine)	Look	100 units/mL	0.5 to 1 unit/kg/day

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