CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-301

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:	October 8, 2008
To:	Donna Griebel, M.D., Director Division of Gastroenterology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Carol Holquist, R.Ph. Director Division of Medication Error Prevention and Analysis
From:	Melina Griffis, R.Ph., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name, Label and Labeling Review
Drug Name(s):	Apriso (mesalamine) Extended Release Capsules, 375 mg
Application Type/Number:	NDA 22-301
Applicant/sponsor:	Salix Pharmaceuticals, Inc.
OSE RCM #:	2008-1327

***Note: This review contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Apriso, 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, Apriso, for this product. 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.

Furthermore, this name must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected action date of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Gastroenterology Products for assessment of the proprietary name, Apriso, regarding potential name confusion with other proprietary or established drug names. The proposed product container labels and insert labeling were provided by the sponsor for our evaluation.

1.2 PRODUCT INFORMATION

Apriso (mesalamine) is a pending NDA with an anticipated action date of October 31, 2008. Apriso is a locally acting aminosalicylate indicated for the maintenance of remission of ulcerative colitis in patients 18 years of age and older. It is available in one strength, 375 mg capsules, and the recommended dose of Apriso is 1500 g/day (4 capsules) to be taken once daily with or without food. The label claims that this product exhibits delayed-release and extended-release properties.

Mesalamine is also marketed under the proprietary names Asacol (400 mg and 800mg tablets), Pentasa (250 mg and 500 mg capsules), Rowasa (4 GM/60 mL enema), Canasa (1 GM suppository), and Lialda (1.2 GM tablets). Generic mesalamine enemas are also available.

2 METHODS AND MATERIALS

This section consists of methods and materials used by medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus for this assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.[1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Apriso, 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 CDER.

For the proprietary name, Apriso, the medication error staff of the Division of Medication Error Prevention and Analysis search a standard set of databases and information sources to identify

names with orthographic and phonetic similarity (see Sections 2.1.1 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). The Division also conducts internal CDER prescription analysis studies (see 2.1.2), 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. [1] 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 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 considers 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, the Division of Medication Error Prevention and Analysis 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.[2]

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 'A' 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.[3][4]

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

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

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

To identify drug names that may look similar to Apriso, the Staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (six letters), upstrokes (one, capital letter 'A'), downstokes (lowercase 'p'), cross-strokes (A), and dotted letters ('i'). Additionally, several letters in Apriso may be vulnerable to ambiguity when scripted, including the letter 'A' may appear as 'Ci, 'Cl' or 'O', lower case 'o' may appear as a lower case 'e' or 'a' and lower case 'p' may appear as 'jo'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Apriso.

When searching to identify potential names that may sound similar to Apriso, the Medication Error Staff search for names with similar number of syllables (three), stresses (A-pri-SO or AP-ri-so), and placement of vowel and consonant sounds. The sponsor'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 (Apriso), the established name (mesalamine) proposed indication (the maintenance of remission of ulcerative colitis), strength (375 mg), dose (4 capsules), frequency of administration (daily), route (oral) and dosage form of the product (capsule). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff generally take into consideration.

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, Apriso, was provided to the medication error staff of the Division of Medication Error Prevention and Analysis 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 Apriso using the criteria outlined in 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 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 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.

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[4] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artifical Inteligence in Medicine (2005)

2.1.1.2 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, Apriso. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the Division of Medication Error Prevention and Analysis 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.

2.1.2 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 Apriso 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 Apriso in 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. 0923C Study (conducted on September 23 , 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order: Apriso 0.375 mg Take 4 capsules by mouth once daily	Apriso 0.375 mg 4 caps po QD

Outpatient Prescription Order:	
Apriso 0.375 mg #120 take 4 caps po daily	

2.1.3 External Proprietary Name Risk Assessment

For this product, the Sponsor submitted a Proprietary Name Safety Assessment conducted by the Drug Safety Institute (DSI) to evaluate the proposed proprietary name Apriso. The Division of Medication Error Prevention conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in the Division's Medication Error Staff's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Sponsor. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the Division of Medication Error Prevention provides a detailed explanation of these differences.

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.[5] 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 then 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

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

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 Apriso 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 Apriso 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 posses 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. The Division of Medication Error Prevention and Analysis 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 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 name and another drug product.

In the event that the Division of Medication Error Prevention and Analysis objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, the Division 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 the Division will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then the Division of Medication Error Prevention and Analysis will not object to the use of the proprietary name. If any of these conditions are met, then the Division 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 IOM, WHO, JCAHO, and ISMP, 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 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, the Division of Medication Error Prevention and Analysis 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 limitations of the process).

If the Division of Medication Error Prevention and Analysis 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. The Division of Medication Error Prevention and Analysis is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for the Division of Medication Error Prevention and Analysis 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 the Division of Medication Error Prevention and Analysis 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.[6]

Because DMEPA staff analyze reported misuse of drugs, DMEPA staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMEPA uses 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.

For this product the Sponsor submitted the following labels and insert labeling for our review (see Appendix K , L, M for images):

- Retail and Physician Sample Container Label
- Physician Sample Carton Labels
- Physician Sample Tray Label
- Package Insert (images not included)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

Our search of the internet, several standard published databases and information sources (see Section 7 References) identified 19 names as having some similarity to the name Apriso: Vaprisol, Apresoline, Aplisol, Apri, Apriza, Optison, Afrinol, Aprocin, Apra, ____ Aspirin, Afrin, Uprima, Avapro, Cipro, Aprela, Apidra, Aprobit, and Aprobal. b(4)

Twelve of the 19 names were thought to look like Apriso (Aprocin, Apra, ____ Aspirin, Afrin, Uprima, Avapro, Cipro, Aprela, Apidra, Aprobit, and Aprobal) and 6 names (Apresoline, Aplisol, Apri, Apriza, Optison and Afrinol) were thought to look and sound similar to Apriso. One name (Vaprisol) was thought to sound like Apriso. b(4)

No USAN stems were identified in Apriso as of September 18, 2008.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention and Analysis staff (see section 3.1.1. above), but did not identify any additional names with similarity to Apriso.

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 32 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About 66% of the participants (n=21) interpreted the name correctly as

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

"Apriso," with correct interpretation occurring more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The majority of misinterpretations occurred in the phonetic prescription study, 3 respondents misinterpreted 'Apriso' as 'Prefill'. In the written prescription studies, the letter 'i' was misinterpreted as 'e' by six respondents. One respondent in the written study misinterpreted 'Apriso' for 'Cipriso' which is similar to the marketed drug Cipro and discussed later in this review. See Appendix A for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Proprietary Name Risk Assessment

In the proposed name risk assessment submitted by the Sponsor, DSI identified and evaluated a total of 89 drug names (Afrin, Afrinol, Apidra, Aplisol, Apra, Apresoline, Apri, Cipro, Avapro, Abilify, Abreva, Aciphex, Aciphex, Acrisorcin, —— , Aerohist, Ahist, AK-Pred, Akpro, Akrinol, Algisorb, Aloprim, Alprazolam, Ambisome, Amrix, Amvisc, Anusol, Apap, —— Aplitest, Appearex, Apptrim, Aprazone, Aprepitant, Apresodex, Aprodine, Aprozide, Aptivus, Aricept, Aricin, Aridol, Aspridox, Asprimox, Atenolol, Atretol, Atridox, Atrohist, Atropisol, Aurasol, Auroto, Aurinol, Avinza, Caprex, —— , Elaprase, Enpresse-28, Epifoam, Episeal, Eprex, Ery-sol, Eycette, I-Prin, Lamotrigine, Marpres, Napril, Naprosyn, Natrico, Pap urea, Perisol, Presate, Precef, Precise, Pressorol, Presun, Primsol, Prestiq, —— Prosof, Prosol, Prosom, Rimso, Sarisol, Singulair, Tearisol, Trisudo, Trisol, Trycet, Trysul and Vaprisol) thought to have some potential for confusion with the name Apriso.

b(4)

Ten of the 89 names (Afrin, Afrinol, Apidra, Aplisol, Apra, Apresoline, Apri, Cipro, Avapro and Vaprisol) were previously identified in the Division of Medication Error Prevention and Analysis Staff searches, the Expert Panel Discussion, or FDA prescription studies.

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look similar to Apriso. As such, a total of 98 names (19 identified by the CDER Expert panel discussion and 79 additional from the DSI report submitted by the sponsor) were analyzed to determine if the drug names could be confused with Apriso 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 Apriso, and thus determined to present some risk for confusion. Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name, Apriso, could potentially be confused with any of the 98 names and lead to medication error. This analysis determined that the name similarity between Apriso and the identified names was unlikely to result in medication errors for all 98 product names for the reasons described in Appendices C-J.

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels, carton labeling and package insert identified several potential sources of medication error.

3.2.1 General Comment

The dosage form is described as 'delayed+extended release capsules'.

3.2.2 Retail and Physician Sample Container Labels and Physician Sample Carton Label (includes peel label)

The product strength appears smaller than the net quantity (both labels).

The graphic logo (dots) immediately follows the proprietary name (both labels).

The established name is less than ½ the size of the proprietary name (both labels).

The net quantity of 120 appears underneath the peel label on the physician carton sample carton which only contains 4 capsules.

The NDC # is located in the middle of the principle display panel.

3.2.3 Package Insert

The dose is expressed as 0.375 g and is inconsistent with the dose of 375 mg as expressed on the product container labels.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

We evaluated a total of 98 names for their potential confusion with Apriso. Our FMEA found the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

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. However, the Division of Medication Error Prevention and Analysis believes that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 123 CDER practitioners, and, in this case, the data submitted by the Sponsor from an independent proprietary name risk assessment firm, which included the responses of frontline practitioners.

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 Division of Medication Error Prevention and Analysis recommends that the proprietary name be re-submitted for review when the NDA is filed and 90 days prior to the goal date.

4.2 LABEL AND LABELING RISK ASSESSMENT

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton and container labels are vulnerable to confusion that could lead to medication errors.

4.2.1 General Comment

The dosage form is described as 'delayed+extended release capsules' throughout the carton labeling and container labels. This is not a recognized dosage form by USP. The dosage form should be designated as "extended-release" as recommended by the Labeling and Nomenclature Committee and review chemist.

4.2.2 Retail and Physician Sample Container Labels and Physician Sample Carton Labeling (includes peel label)

The product strength appears smaller than the net quantity and should be increased in prominence and immediately precede the proprietary name if possible to avoid confusion of these numbers. Additionally, the net quantity statements should be relocated to the bottom of the principle display panel on these labels.

The location of the graphic (blue dots) immediately follows the Apriso name and is not appropriate since it is located in close proximity to the proprietary name. These attributes make the graphic more prominent than other critical information and therefore, the graphic should be relocated to a less prominent location on the label.

In accordance with 21 CFR 201.10(g)(2), the established name on all labels must be at least ½ the size of the proprietary name.

In accordance with 21 CFR 207.359(b)(3)(i), the NDC number shall appear prominently in the top third of the principle display panel. Although, the NDC number is close to the top third of the principle display panels on these labels, we would recommend relocating it above the Apriso name.

The net quantity of 120 underneath the peel label on the physician carton sample carton label should be deleted since only 4 capsules are in this container.

4.2.3 Package Insert

The product strength is expressed as 0.375 g throughout the package insert, however, it is expressed as 375 mg on the immediate product labeling. It is recommended for consistency that the product strength on all labels be represented in the same unit measurement. Ideally, in this case DMEPA would recommend expressing the dose as 375 mg since the mg designation is more conventional than the gram designation.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Apriso, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Apriso, for this product.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Errors Prevention 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 Cherye Milburn, Project Manager, at 301-796-2084.

1. The Division of Medication Error Prevention and Analysis has no objection to the use of the proprietary name Apriso for this product. 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 day from the date of this review, the proposed name must be resubmitted for evaluation.

2. The dosage form is described as 'delayed+extended release capsules' throughout the carton labeling and container labels. The dosage form should be designated as 'extended-

release' as recommended by the Labeling and Nomenclature Committee and review chemist.

5.2 COMMENTS TO THE APPLICANT

5.2.1.1 Proprietary Name

The Division of Medication Error Prevention and Analysis has no objections to the use of the proprietary name Apriso for this product. However, your name will be reevaluated 90 days prior to approval and if any of the proposed product characteristics are altered.

5.2.1.2 Retail and Physician Container Labels and Physician Sample Carton Label (includes peel label)

1. The product strength appears smaller than the net quantity and should be increased in prominence and immediately precede the proprietary name if possible to avoid confusion of these numbers. Additionally, the net quantity statements should be relocated to the bottom of the principle display panel on these labels.
2. The location of the graphic (blue dots) immediately follows the Apriso name and is not appropriate since it is located in close proximity to the proprietary name. These attributes make the graphic more prominent than other critical information and therefore, the graphic should be relocated to a less prominent location on the label.
3. In accordance with 21 CFR 201.10(g)(2), the established name on all labels must be at least ½ the size of the proprietary name.
4. In accordance with 21 CFR 207.359(b)(3)(i), the NDC number shall appear prominently in the top third of the principle display panel. Although, the NDC number is close to the top third of the principle display panels on these labels, we would recommend relocating it above the Apriso name.

5.2.1.3 Package Insert

The product strength is expressed as 0.375 g throughout the package insert, however, it is expressed as 375 mg on the immediate product labeling. It is recommended for consistency that the product strength on all labels be represented in the same unit measurement. Ideally, in this case DMEPA would recommend expressing the dose as 375 mg since the mg designation is more conventional than the gram designation.

REFERENCES

1. Micromedex Integrated Index (http://csi.micromedex.com)

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

2. 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.

3. 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.

4. AMF Decision Support System [DSS]

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

5. 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.

6. 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.

7. 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.

8. U.S. Patent and Trademark Office (http://www.uspto.gov)

Provides information regarding patent and trademarks.

9. 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.

10. 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.

11. 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.

12. 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.

13. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

15. Lexi-Comp (www.lexi.com)

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

16. 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. The Division of Medication Error Prevention and Analysis 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 lead 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 Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, the Division of Medication Error Prevention and Analysis 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
	Similar spelling	Identical prefix	• Names may appear similar in

Look-alike		Identical infix Identical suffix Length of the name Overlapping product characteristics	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 Upstokes Downstrokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses- Apriso Study 0923C

Inpatient Medication Order	Voice Prescription	Outpatient Prescription Order
Apreso	Apriso	Apriso
Apriso	Prefill	Apriso
Apreso	Apriso	Apriso

Apriso	Prefill	Apriso
Apriso	Apreso	Apriso
Cipriso	Prefill	Apriso
Apriso		Apriso
Apriso		Apriso
Apriso		Apriso
Apriso		
Dipreso		
Apriso		
Apreso		
Apreso		
Apriso		
Apreso		
Apriso		

Appendix C: Names lacking convincing orthographic and/or phonetic similarities with Apriso

Proprietary Name	Similarity to Apriso	Proprietary Name	Similarity to Apriso
Apresoline	Look & Sound Alike	I-Prin	
Abilify		Lamotrigine	
Aciphex		Marpres	
Acrisorcin		Atrohist	
[redacted]		Atropisol	
Aerohist		Aprepitant	
Control		Apptrim	
Elaprase		Appearex	
Enpresse-28		Aplitest	
Ery-Sol		[redacted]	
Erycette		Apresodex	

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Aprodine	DSI	Akrinol	
Aprozide		Algisorb	
Aricept		Aloprim	
AK-Pred		APAP	
Alprazolam		Ambisome	
Napril		Naprosyn	
Perisol		Pap Urea	
Presate		Primsol	
Precef		Prestiq	
Pressorol		Prosof	
[redacted]		Prosol	
Sarisol		Aridol	
Asprimox		Aspridrox	
Atenolol		Atretol	
Atridox		Singulair	
Tearisol		Trisudo	
Trycet		Trisol	
Trysul			

b(4)

Appendix D: Names of products not considered to be pharmaceuticals

Proprietary Name	Type of Product
Apriza (DSI)	All purpose hard surface cleaner
Aprobal	Toxic chemical substance; listed in Micromed and unable to locate in any other commonly

	used pharmaceutical database
Aprobit	Toxic chemical substance; listed in Micromed and unable to locate in any other commonly used pharmaceutical database

Appendix E: Unapproved Proposed Proprietary name

Proposed Proprietary Name	Status
Aprela (conjugated estrogen) (OSE review 2006-1144	IND currently active

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Appendix F: Names of Discontinued or Withdrawn Products

Proprietary Name	Status
Caprex (capsaicin)	Product Discontinued; generics are available
Aurasol(colloidal gold)	Product Discontinued; no generics
Aurinol (chloroxylenol & acetic acid with benzalkonium chloride) Otic	Product Discontinued; no generics
Aprazone (sulfinpyrazone)	Product Discontinued; generics are available

Aricin (triamcinolone)	Product Discontinued; generics are available
Akpro (dipivefrin HCl) Ophthalmic Drops	Product Discontinued; generics are available
Natrico (potassium nitrate) Granules	Product Discontinued; no generics are available
Precise Pregnancy Test Kit	Product Discontinued; other kits available in marketplace
Prosom (estazolam)	Product Discontinued; generics are available

Appendix G: Names of Products Marketed in a Foreign Country

Proprietary Name	Status
Uprima (apomorphine)	Available in Europe; marketed in US under the tradename Apokyn
Aprocin (ciprofloxacin)	Available in Bangladesh

Appendix H: Products with no overlap in strength and usual dosage

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Apriso (mesalamine) Capsules		375 mg	1500 mg (4 capsules) once daily
Amrix (cyclobenzaprine)	—	15 mg and 30 mg	15 mg to 30 mg once daily

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Capsules			
Eprex (epoetin alfa)	—	500 u/0.25 mL, 1000u/0.5 mL, 2000 u/0.5 mL, 3000 u/0.3 mL, 4000 u/0.4 mL, 10,000 u/mL and 40,000 u/mL	75 to 150 u once to 1-3 times weekly
Avapro (irbesartan) Tablets	Look alike	75 mg, 150 mg and 300 mg	150 mg to 300 mg once daily
Cipro (ciprofloxacin)	Look alike	100 mg, 250 mg 500 mg, and 750 mg tablets 250 mg/5 mL and 500 mg/5 mL oral suspension 200 mg/20 mL and 400 mg/40 mL intravenous	125 mg to 1200mg given 2 to 3 times daily
Aspirin	—	81 mg, 325 mg and 500 mg Tablets	81 to 500 mg up to every 4 to 6 hours (2000 mg/day maximum dose)
Anusol (hydrocortisone)	—	1% and 2.5 % Cream or Ointment 25 mg Suppositories	Use as directed 2-6 times daily
Avinza (morphine sulfate)	—	30 mg, 60 mg, 90 mg, and 120 mg extended release oral capsules	30 mg to 120 mg once daily in a single dose

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Appendix I: Potential confusing name with overlap in single strength availability but no overlap in any other product characteristics

Product name with potential for confusion	Indication	Usual Dose and Setting for Use (if applicable)
Apriso (mesalamine) 375 mg capsules	Maintenance of Ulcerative Colitis Remission	1500 mg (4 capsules) once daily
Rimso (dimethyl sulfoxide) 50 % Aqueous Solution	IV Solution for bladder instillation	Dose is patient dependant but given every 2 weeks

Presun (padimate O /oxybenzone) Sunscreen	Prevention of sunburn	Apply prior to exposure to the sun and re-apply after 2 hours
Auroto Otic Drops	Treatment of ear pain	2 drops 3 to 4 times daily in affected ear(s)
Episeal Topical Dressing	For wound closure	Use as needed for wound closure
Afrin (oxymetazoline) Nasal Spray	Treatment for nasal congestion	Use 2 to 6 sprays in nostril(s) twice daily
Apidra (insulin glulisine) 100 units/mL	Treatment of hypoglycemia in diabetic patients	Dose is dependant on patient individual needs
Vaprisol (conivaptan HCl) 20 mg/mL intravenous injection	Inpatient treatment for euvolemic hyponatremia	20 mg given intravenously once daily; for inpatient use
Aplisol (tuberculin purified protein derivative)	For intradermal placement of PPD test	Single dose administered for PPD test
Abreva (docosanol) 10 % Cream	OTC topical cream for treatment of cold sores	Apply 1 to 5 times daily
Amvisc (sodium hyaluronate) 1.6 % (0.5 mL or 0.8 mL syringe)	For use in during ophthalmic surgery	Varies per patient; used in a clinical setting only
Optison (albumin human) 10 mg/mL	For contrast enhancement during ultrasound imaging	Based on patient weight

Appendix J: Potential confusing name with overlap in single strength availability

Apriso (mesalamine) 375 mg capsules	375 mg	1500 mg (4 capsules) once daily
Failure Mode: Name confusion	**Causes (could be multiple)**	**Effects**
Apra (paracetamol) 160 mg/5 mL (located in Fact & Comparisons, unable	Orthographic similarity (names both have 'Apr' the same position) Both products available in	Orthographic differences in the suffix of the name along with differences in the products characteristics minimize the likelihood of medication error in the usual practice setting.

to locate in any other drug sites)	single strength only	Rationale: Apra is a pediatric oral solution available as an OTC for the treatment of fever. Additionally, orthographic differences are introduced since Apra only contains 4 letters instead of 6 and 'a' differs from 'iso'.
Acuprin (aspirin) 81 mg Tablets	Orthographic similarity (names both begin with letter 'A' and have similar shapes) Both products available in single strength only	Orthographic differences in the suffix of the name along with differences in the products characteristics minimize the likelihood of medication error in the usual practice setting. Rationale: Acuprin is an OTC for the treatment of fever and pain and recommended to be administered every 4 to 6 hours in contrast to Apriso which is once daily. Additionally, orthographic differences are introduced since Acuprin contains one additional letter and the position of the 'p' is towards the end of the word instead of at the beginning position as is the case in Apriso.
Apri (desogestrel/ethinyl estradiol 0.15/0.03 mg) Tablets	Orthographic similarity (names both have 'Apr' the same position) Both products available in single strength only	Orthographic differences in the suffix of the name along with differences in the products characteristics minimize the likelihood of medication error in the usual practice setting. Rationale: Apri is an oral contraceptive taken once daily. Orthographic differences are introduced since Apri only contains 4 letters instead of 6 and 'i differs from 'iso'.
Afrinol (psuedoephedrine sulfate) 120 mg	Orthographic similarity (names both have 'A', 'r', 'i' and 's' in the same position) Both products available in single strength only	Orthographic differences in the name along with differences in the products characteristics minimize the likelihood of medication error in the usual practice setting. Rationale: Orthographic differences are introduced since Afrinol has 2 additional upstokes ('f' and 'l') and contains 1 more letter than Apriso. Additionally, Afrinol is available as an OTC and administered twice daily.
Aptivus (tipranavir) 250 mg Capsules	Orthographic similarity (names both have 'Ap' and 'i' in the same position) Both products available in single strength only	Orthographic differences in the suffix of the name along with differences in the products characteristics minimize the likelihood of medication error in the usual practice setting. Rationale: Orthographic differences are introduced since Aptivus has 1 additional upstoke ('t'), and contains 1 more letter than Apriso. Additionally, Aptivus is indicated for the treatment of HIV and is administered twice daily instead of once daily.
Epifoam (hydrocortisone 1%/pramoxine 1%) Aerosol Foam	Orthographic similarity (names both have similar shapes) Both products available in single strength only	Orthographic differences in the suffix of the name along with differences in the products characteristics minimize the likelihood of medication error in the usual practice setting. Rationale: Orthographic differences are introduced since Epifoam has 1 additional upstoke ('f'), contains 1 more

		letter than Apriso and begins with the letter 'E' instead of 'A'. Additionally, Epifoam is administered rectally 2-3 times daily.
Ahist (chlorpheniramine tannate) 12 mg tablets	Orthographic similarity (names both share 'A', 'i' and 's' in similar positions) Both products available in single strength only	Orthographic differences minimize the likelihood of medication error in the usual practice setting. Rationale: Orthographic differences are introduced since Ahist has 2 additional upstokes ('h' and 't'), does not contain a downstoke (Apriso has lowercase 'p') and contains 1 less letter than Apriso.

<u>Appendix K:</u> Container Labels

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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DRUG SAFETY OFFICE REVIEWER

Carol Holquist
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DRUG SAFETY OFFICE REVIEWER