CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-918

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:	March 16, 2009
To:	Wiley Chambers, MD Acting Director, Division of Anti-Infective and Ophthalmology Products (DAIOP)
Through:	Todd Bridges, RPh, Team Leader Denise P. Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
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Subject:	Proprietary Name Review
Drug Name(s):	Cetraxal (Ciprofloxacin Otic) Solution, 0.2%
Application Type/Number:	NDA# 21-918 (IND# 67,173)
Applicant:	Salvat, S.A.
OSE RCM #:	2008-1964

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

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EXECUTIVE SUMMARY

The proposed name, Cetraxal was previously reviewed in 2005 with no objections and since the application is 90 days prior to approval we re-reviewed the proposed name. None of the product characteristics have been revised since our last review. Forty-two new names were identified as having some similarity to the proposed name but our FMEA indicates the name Cetraxal is not vulnerable to confusion with these names. Additionally, neither DDMAC or the Division of Anti-infective and Ophthalmology Products (DAIOP) had objections to the name. As such, we have no objections to the use of the name, Cetraxal, for this product.

1 BACKGROUND

1.1 INTRODUCTION

This re-review of the proposed name, Cetraxal, was written in order to rule out any objections to the proposed proprietary name since the signature date of the previous DMEPA review. The vial label, carton labeling, outer wrap foil pouch and insert labeling were submitted for review and comment and these will be evaluated under a separate forthcoming review (OSE# 2008-1965).

1.2 PRODUCT INFORMATION

Cetraxal® (Ciprofloxacin Otic Solution) is a broad-spectrum fluoroquinolone antibacterial agent indicated for the treatment of acute otitis externa in adult and pediatric patients, one year and older, due to susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The dose is the contents of one unit-dose vial (0.25 ml) instilled into the affected ear(s) twice daily for seven days. Cetraxal® is supplied as fourteen plastic, unit-dose vials in — foil — — foil pouch contains — twist top vials and each vial contains 0.25 ml of Ciprofloxacin Otic Solution. The vials are attached to one another and form a strip. b(4)

1.3 REGULATORY HISTORY

In our previous review (OSE# 05-0132) dated January 10, 2006, DMEPA had no objection to the proposed proprietary name, Cetraxal. However, we did not recommend the use of the proposed low density polyethylene (LDPE) vials for this product due to the potential for confusion with inhalation products and the increased risk of wrong route of administration errors.

The Division of Anti-Infective and Ophthalmology Products (DAIOP) issued an Approvable Letter for NDA 21-918 on April 6, 2006 contingent on the Applicant providing a new vial configuration, stability information for the new vial and any applicable label and labeling changes. On October 31, 2008 the Applicant provided a complete class 2 response to the Approvable Letter.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA staff to conduct a proprietary name risk assessment. The primary focus for this assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

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

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for details) and held a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). DMEPA also conducts internal CDER prescription analysis studies. When provided, external prescription analysis study results are considered and incorporated into the overall risk assessment.

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 2.1.5). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [3] DMEPA 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 DMEPA 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, DMEPA 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.[4]

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[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/aboutMedErrors.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

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

For this review, particular consideration was given to drug names beginning with the letter 'C' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the United States Pharmacopeia-Institute of Medication Practices (USP-ISMP) Medication Error Reporting Program involve pairs beginning with the same letter.[5,6]

To identify drug names that may look similar to Cetraxal, the DMEPA staff also considers the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (8 letters), upstrokes (3, capital letter 'C', lower case 't' and 'l'), down-strokes (none), cross-strokes (lower case 't' and 'x'), and dotted letters (none). Additionally, several letters in Cetraxal may be vulnerable to ambiguity when scripted, including the letter 'C' may appear as an 'L'; lower case 'e' may appear as a lower case 'i' or 'l'; lower case 't' may appear as a lower case 'x' and vice versa; lower case 'r' may appear as a lower case 'c' or 'n'; lower case 'a' may appear as a 'c' or the combination letters '-ci-' and lower case 'l' may appear as a lower case 'b' or an 'e'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Cetraxal.

When searching to identify potential names that may sound similar to Cetraxal, the DMEPA staff search for names with similar number of syllables (3), stresses (ce-TRAX-al or ce-trax-AL), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary such as the letter 'c' may sound like an 's' and the letter 'x' may sound like the combination letters '-ks-'. Although the Applicant's intended pronunciation of the proprietary name is "sĭ – trĭks – ōl" (as in the word "all"), the Division of Medication Error Prevention and Analysis notes that names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

The DMEPA staff also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, the following information was provided about the proposed product to the medication error staff: proposed proprietary name (Cetraxal), the established name (ciprofloxacin otic solution), proposed indication (treatment of acute otitis externa in adults and pediatric patients 1 year old and older, due to susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*), strength (0.2%), dose (contents of one unit-dose vial (0.25 mL), frequency of administration (twice daily), route (affected ear(s)), dosage form of the product (otic solution) and duration of use (seven days). Appendix A provides a more detailed listing of the product characteristics the medication error staff generally takes into consideration.

Lastly, the DMEPA staff also considers the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this

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

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

assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

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

2.1.1.2 CDER Expert Panel Discussion

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

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

2.1.2 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 the proposed proprietary name 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 (one hundred twenty-three) 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 the proposed proprietary name 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 DMEPA.

Figure 1. Cetraxal Prescription Study (conducted on January 5, 2009)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Outpatient Prescription: Cetraxal #1 place 1 drop into affected ear(s) bid x 7 days	"Cetraxal #1 – place one drop into affected ears twice daily for 7 days"
Inpatient Medication Order: Cetraxal #1 [illegible] affected ear(s) bid x 7 days	

2.1.3 Adverse Events Reporting System (AERS) Selection of Cases

On February 20, 2009, the Division of Medication Error Prevention and Analysis searched the FDA Adverse Event Reporting System (AERS) to retrieve any post marketing reports associated with Cetraxal since this drug product is available outside of the U.S. AERS was searched using the trade name "Cetraxal", the established name "ciprofloxacin", the route of administration "auricular (otic)", the MedDRA high level group term (HLGT) "Medication Errors" and preferred term (PT) "Pharmaceutical Product Complaint".

The reports were manually reviewed to exclude duplicate reports as well as reports that did not describe a medication error. The cases that described a medication error were categorized by type of error. We excluded the types of errors associated with risks that would not translate to review of the proposed name, Cetraxal, and we reviewed the cases within each category to identify contributing factors.

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 applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode 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

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

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 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 Cetraxal 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 Cetraxal 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 possesses 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.

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

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, <u>and</u> 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 a USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. DMEPA identifies a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

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

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then DMEPA 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 (IOM), World Health Organization (WHO), The Joint Commission (TJC), and the Institute of Safe Medication Practices (ISMP), who have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval.

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

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and 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 approving the error-prone proprietary name. Moreover, even after Applicants have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error which would render the proposed name acceptable.