

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-918

OTHER 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 31, 2009

To: Wiley Chambers, MD
Acting Director, Division of Anti-Infective and Ophthalmology
Products (DAIOP)

Through: Todd Bridges, RPh, Team Leader
Denise F. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Denise V. Bough, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling 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 #: 2008-1965

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EXECUTIVE SUMMARY

This consult was written in response to a request from the Division of Anti-Infective and Ophthalmology Products for assessment of the label, labeling and outer wrap foil pouch for Cetraxal. DMEPA had no objections to the proposed proprietary name, Cetraxal, (OSE# 2008-1964 dated March 16, 2009). Cetraxal (Ciprofloxacin Otic Solution) is a fluoroquinolone antibacterial agent indicated for the treatment of acute otitis externa in pediatric (age 1 year and older) and adult patients due to susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The dose is the contents of one unit-dose container (0.25 ml) instilled into the affected ear(s) twice daily for seven days.

Using Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container label, carton labeling, outer wrap foil pouch and insert labeling to identify vulnerabilities that could lead to medication errors. Our findings indicate that the design and the presentation of information on the proposed labels, labeling and outer wrap foil pouch appear to be vulnerable to confusion that could lead to medication errors. We specifically note that the principal display panel is cluttered because of too much information and the directions for use in the insert labeling are incomplete and may lead to inappropriate use of this product. Furthermore, we remain concerned about the packaging of Cetraxal in LDPE vials (see Appendix E) and the potential that this configuration may cause confusion and increase the risk of wrong route of administration errors associated with this product. To address these concerns, the Applicant has embossed the word 'ear' on one side of the vial along with the established name and strength. Although we remain unsure of the effectiveness of this strategy since embossed information is difficult to read on LDPE material, DMEPA aligns with the Division to allow the marketing of this product as it is currently proposed.

See Section 3 for the risks which we have identified that can be addressed and mitigated prior to drug approval and for our recommendations which aim to reduce the risk of medication errors. 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 correspondence to the Applicant pertaining to this issue. If you have further questions or need clarifications, please contact Marlene Hammer, OSE Project Manager, at 301-796-0757.

1 REGULATORY HISTORY

In our previous review (OSE# 05-0132) dated January 10, 2006, DMEPA did not recommend 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.

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

2 MATERIALS REVIEWED

For this product the Applicant submitted on December 19, 2007, the following labels and labeling for DMEPA to review (see Appendices A through E for images):

- Carton Labeling for 14 single-use containers
- Container pouch foil for 14 single use containers
- Sample Carton Labeling for 2 single use containers
- Container pouch foil for 2 single use containers
- Low density polyethylene (LDPE) Packaging Configuration
- Prescribing Information (no image)

Additionally, the Applicant submitted a sample of the revised pouch foil with the LDPE packaging configuration on February 11, 2009, as a result of our e-mail request on February 3, 2009. This latest submission is included in this review.

3 RECOMMENDATIONS

We request the following recommendations be communicated to the Applicant prior to approval.

3.1 COMMENTS TO THE APPLICANT

The Division of Medication Error Prevention and Analysis has identified areas in need of improvement. The comments are listed below.

3.1.2 *Foil Pouch Labeling*

DMEPA notes the differences in the format of the labeling submitted on December 19, 2007 versus the working sample submitted February 11, 2009 (see Appendix B). We prefer the format of the latter submission (February 11, 2009) and recommend you revise this labeling such that the section titled 'Directions for Use' appears before the list of ingredients. This sequence of information should occur on both the trade and sample pouch foils.

3.1.3 *Insert Labeling*

1. Delete the adjectives 'Sterile, preservative-free' under Dosage Forms and Strengths (Section 3) since this information does not describe a dosage form or strength and is not consistent with 21 CFR 201.57(e)(4).

b(4)

1. Statements such as 'Not for Ophthalmic Use', 'Not for Inhalation' and 'Not for Injection' may inadvertently encourage wrong routes of administration due to the reader's focus on the route of administration and overlooking the word 'not'. We are aware of previous recommendations to revise these statements to a bold font, but after discussion, we are in agreement that this may actually have unintentional consequences. Therefore, we recommend that you delete these statements in the warnings and precautions section.
2. To complete the 'Directions for Use' administration directions (section 17.1) we recommend you add a statement advising the patient to follow the same instructions for instilling the medication into the alternate ear (if warranted). This statement should come after the patient is instructed to 'Maintain this position . . . into the ear'. The statement should read 'Repeat, if necessary, for the opposite ear' which is consistent with what is stated in the 'Dosage and Administration' section.
3. To ensure the patient administers the entire dose intended, we recommend you revise the statement ' _____ which currently appears under 'Directions for Use' (section 17.1) to 'Lie with the affected ear upward and then instill the entire contents of one container into the ear'.
4. Further define twice daily (e.g., "...the affected ear twice daily [about 12 hours apart, for example 8 AM and 8 PM] for seven days") to help ensure the product is dosed as intended.
5. To maintain consistency with the carton labeling, add the statement 'discard container after use' in Section 16 'How Supplied/Storage and Handling'.
6. To minimize the risk of information being overlooked, reformat the sentences under 'Directions for Use' such that the pictures come at the end of the sentence and the sentences are not fragmented.
7. Add a 'discard' statement in the 'How Supplied' Section so that patients know what to do with the containers after administering the drops. This statement should be similar to the one on the foil pouch (e.g., 'Throw used container and top away immediately because . . .').

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4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Other Reviews- 1

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/s/

Denise Baugh
3/31/2009 04:17:37 PM
DRUG SAFETY OFFICE REVIEWER

Todd Bridges
3/31/2009 04:38:41 PM
DRUG SAFETY OFFICE REVIEWER

Denise Teyer
4/1/2009 11:31:45 AM
DRUG SAFETY OFFICE REVIEWER