

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Cetraxal, the primary concerns raised were related to look-alike and/or sound-alike confusion with Citracal, Citrucel, and Trexall. Additionally, DMETS is concerned with the proposed packaging configuration.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, one respondent in the outpatient prescription study interpreted the proposed proprietary name as Ataraxal and nine additional respondents from the same study interpreted the name as Atraxal. Ataraxal and Atraxal can potentially look similar to the currently marketed U.S. product Atarax. Despite this finding, Atarax was not further reviewed due to a lack of convincing look-alike and sound-alike similarities with Cetraxal, in addition to differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration, and dosage form. The majority of interpretations were misspelled/phonetic variations of the proposed name, Cetraxal.

1. Look-Alike/Sound Alike Assessment

- a. Citracal was identified to have look and sound-alike similarities to the proposed name, Cetraxal. Citracal is the brand name of an over-the-counter dietary supplement product line. The line of Citracal products includes Citracal 200 mg tablets, Citracal 250 mg + D caplets, Citracal 315 mg + D caplets, and Citracal Plus with Magnesium tablets. Each product in the line contains calcium citrate as the primary ingredient. Citracal is indicated for the treatment of osteoporosis, osteomalacia, rickets, latent tetany, and typical premenstrual syndrome symptoms. The usual dose is 1 to 2 tablets (or caplets) twice daily.

Citracal and Cetraxal share similar letters ("Cit..." vs. "Cet...") in the first syllable and the same two letters (A, L) in the last syllable, which contributes to the look-alike and sound-alike similarities between the two names. Additionally, both names contain three syllables and eight letters. Although the names share the middle letters "ra", the differing sixth letter ("c" vs. "x") gives each drug name some orthographic and phonetic distinction (see sample below).

Citracal
Cetraxal

It is not uncommon to see prescribers write prescription orders for over-the-counter products such as Citracal as reminders for patients. Even if this occurs, the potential for medication errors between these two products will be minimized since either a strength and/or modifier will be necessary before dispensing of Citracal. For example, the various formulations of Citracal require an order for Citracal to include a strength (e.g., 200 mg) or a modifier (e.g., "250 mg + D" or "Plus with Magnesium") before dispensing can occur. If such a strength or modifier is not present on an order then the pharmacist would have to call and obtain the missing information from the prescriber. Post-marketing experience has

demonstrated that modifiers are routinely omitted, thus DMETS is concerned that an order for Citracal with the modifier inadvertently omitted may be misinterpreted as an order for Cetraxal. However, in this scenario, the two products have differing directions for use may aid in differentiating Citracal from Cetraxal on a prescription. The usual dose for Citracal is 1 to 2 tablets (or caplets) twice a day while the usual dose for Cetraxal is the contents of one vial instilled into the affected ear(s) twice daily for seven days. However, over-the-counter products such as Citracal are often written with a general direction for use (e.g., "as directed"). Although a prescriber may order Citracal with "as directed" directions for use, a prescription for Cetraxal will likely include detailed directions for use (i.e., one vial instilled into the affected ear twice daily for seven days). Thus, detailed directions for Cetraxal use indicated on a prescription may lessen any confusion stemming from similarities involving this name pair. Furthermore, the two drug products have a different route of administration (orally vs. topical application into the ear canal). Additionally, it is likely that a prescriber ordering an otic preparation will indicate the affected ear(s) on an order by use of a Latin abbreviation ("AS", "AD" or "AU") in the directions for use. Citracal and Cetraxal also differ in how supplied (14 vials vs. 60 tablets, 100 tablets etc.), nature of treatment (chronic vs. acute), product strength (multiple vs. one non-overlapping strength of 0.2%), indication for use (calcium supplementation vs. otic infection), dosage form (tablets or caplets vs. otic solution), dosing units (tablet or caplet vs. vial), and prescription status (over-the-counter vs. prescription). Overall, different product characteristics such as the directions for use and route of administration will minimize the potential for error and confusion between Citracal and Cetraxal.

- b. Citrucel may look and sound similar to Cetraxal when scripted or spoken. Citrucel is an over-the-counter bulk-producing laxative. The usual dose is one heaping tablespoonful in 8 ounces of cold water or 4 tablets one to three times daily.

Citrucel and Cetraxal may sound similar and look similar because both names share similar beginning letters ("Citr..." vs. "Cetr...") and similar ending letters ("...el" vs. "...al"). Orthographic and phonetic similarities may also be attributed to the fact that both drug names contain eight letters and three syllables. However, the names have two differing middle letters ("uc" vs. "ax") that may help in distinguishing the names when scripted (see sample below).

Cetraxal
Citrucel

Additionally, the two products have differing directions for use which may aid in distinguishing Citrucel from Cetraxal on a prescription. The usual dose for Citrucel is one heaping tablespoonful in 8 ounces of cold water or 4 tablets one to three times daily, while the usual dose for Cetraxal is the contents of one vial instilled into the affected ear(s) twice daily for seven days. However, over-the-counter products such as Citrucel are often written with a general direction for use (e.g., "as directed"). Although a prescriber may order Citrucel with "as directed" directions for use, a prescription for Cetraxal will likely include detailed directions for use (i.e., one vial instilled into the affected ear twice daily for seven days). Thus, detailed directions for Cetraxal use indicated on a prescription may lessen any

confusion stemming from similarities involving this name pair. Furthermore, the two drug products have a different route of administration (orally vs. topical application into the ear canal). Additionally, a prescriber ordering an otic product will usually indicate the affected ear(s) on an order by use of a Latin abbreviation ("AS", "AD" or "AU") in the directions for use. The inclusion of this additional information on an order may decrease the potential for name confusion between Citrucel and Cetraxal. Moreover, there are some product characteristics may help to differentiate these two products. They include ordered quantity (14 vials vs. 164 tablets or 245 grams, 480 grams, etc.), nature of treatment (chronic vs. acute), indication for use (constipation vs. otic infection), route of administration (orally vs. topical application into the ear canal), dosage formulation (powder or tablets vs. otic solution), dosing units (tablet or tablespoonful vs. vial), and prescription status (over-the-counter vs. prescription). Overall, differences in the orthographic and phonetic characteristics between the two names and different product characteristics minimize the potential for medication errors between the two names.

- c. Trexall may sound similar to Cetraxal when spoken. Trexall is indicated for the treatment of various cancers, psoriasis, and rheumatoid arthritis. Trexall is available as 5 mg, 7.5 mg, 10 mg, and 15 mg tablets. The endings of each name can sound similar ("all" vs. "al") and both names have similar preceding letter combinations ("Trex..." vs. "...trax") which are the primary contributions to the sound-alike characteristics of this name pair. However, the first syllable of Cetraxal gives the name a distinct sound from the name Trexall. Also, because Trexall is supplied in multiple strengths (5 mg, 7.5 mg, 10 mg, and 15 mg), a strength would need to be indicated on a prescription prior to filling and dispensing the medication, unlike Cetraxal, which is available in only one strength (0.2%). Thus, the necessity of a strength on Trexall prescriptions will help to differentiate the two drug names. Moreover, Trexall and Cetraxal have many differentiating product characteristics such as nature of treatment (chronic vs. acute), product strength (5 mg, 7.5 mg, 10 mg, and 15 mg vs. 0.2%), indication for use (cancer, psoriasis or rheumatoid arthritis vs. otic infection), frequency of administration (daily, weekly or three consecutive doses vs. twice daily), route of administration (orally vs. topical application into the ear canal), dosing units (tablet vs. vial), and dosage formulation (tablet vs. otic solution). Even though the two drug names have similar sound-alike characteristics, DMETS believes the above mentioned "Ce..." sound in Cetraxal combined with product and strength differences help decrease the risk for confusion and error between Trexall and Cetraxal.

2. Safety of Proposed Low Density Polyethylene (LDPE) Packaging Configuration

DMETS is concerned that the packaging of Cetraxal in LDPE plastic vials may lead to confusion and increase the risk of wrong route of administration errors associated with this product. As evidenced by post-marketing reports, health care practitioners as well as patients may associate certain package configurations with particular routes of administration. For example, most ear drop products have traditionally been associated with the two-piece dropper bottles (see Figure 2 page 9) while products packaged in low-density polyethylene (LDPE) plastic vials are typically associated with inhalation drug products (see Figure 3 page 9).

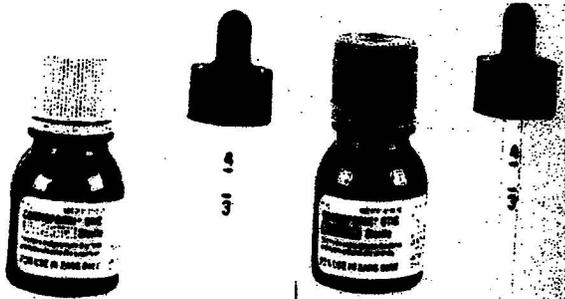


Figure 2. Cortisporin Otic two-piece dropper bottles.

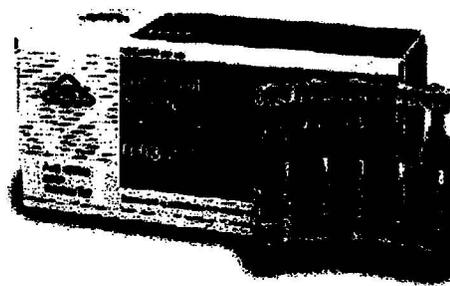


Figure 3. Albuterol for nebulization packaging.

Additionally, drug products packaged in LDPE plastic vials may be more easily confused with one another since few have distinguishing characteristics traditionally utilized on medication containers such as paper labels, color, etc. (see Figure 4 below). Furthermore, the embossed/debossed lettering on LDPE vials is often difficult to read if not illegible. Although the use of embossed/debossed label information addresses the concern for drug product contamination by the volatile components of the paper label, it also creates an opportunity for medication errors. The fact that these vials are difficult to read is a concern that has been voiced by numerous practitioners, patients, and caregivers. Even if the plastic ampules are individually foil-wrapped and the foil contains essential information such as the product name and strength, there is still going to be the problem of unused, loosely stored plastic ampules that are difficult to read and error-prone. Thus, to aid in preventing errors associated with the use of this product, DMETS recommends that sponsor consider an alternative packaging configuration for Cetraxal.



Figure 4. LDPE plastic vials containing a variety of medications.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Cetraxal, DMETS has attempted to focus on safety issues relating to possible medication errors. However, copies of the labels and labeling were provided in black and white, and may not represent the true color of the labels and labeling. Therefore, DMETS cannot assess if there are any safety concerns due to the colors utilized on the labels and labeling. Please forward copies of the revised labels and labeling, in color and reflective of the presentation that will actually be used in the marketplace, when they are available. Additionally, patient information is referenced on the foil pouch and carton labeling but was not submitted for review and comment. Please forward the patient information for review and comment when it becomes available. Upon review of the draft black and white labels and labeling, DMETS has identified the following areas

of improvement, in the interest of minimizing user error and maximizing patient safety.

A. GENERAL COMMENTS

1. DMETS has learned through post-marketing reports of confusion with LDPE packaging, that the embossed/debossed lettering is difficult to read once removed from the foil overwrap. Multiple vials in a single foil wrap lend itself to removal or tearing also affecting the legibility of the foil overwrap itself. Thus, we recommend each vial be individually overwrapped to maintain the legibility of the product name and strength.
2. DMETS does not recommend the use of the container closure system for anything other than pulmonary products. Post-marketing confusion has arisen from the illegible container labels/labeling of drugs packaged in LDPE vials. We have also seen errors across product lines (e.g., oral, pulmonary, and ophthalmic). Thus, to minimize this confusion we recommend not using this packaging configuration for otic solutions.
3. To help ensure the correct route of administration, revise "otic" to read "OTIC" (i.e., all capital letters) and increase the prominence of the statement "For use in ears only". Additionally, include a pictorial of an ear (see Figure 5 below) to minimize inadvertent administration of this otic preparation into the eye or by inhalation.

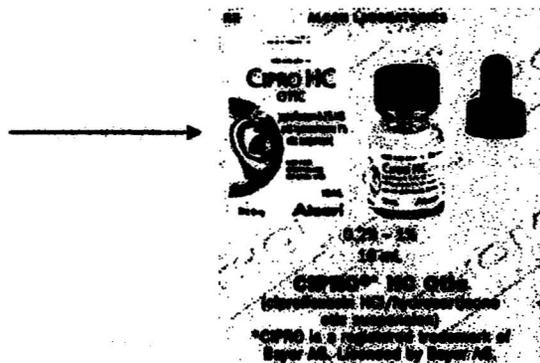


Figure 5. Cipro HC OTIC carton labeling with a large pictorial of an ear on the principal display panel.

b(4)

4. To avoid confusion, delete "deliverable volume" throughout the labeling.
5. In the insert labeling, the container is referred to as " _____ " within DESCRIPTION, _____ within INFORMATION FOR PATIENTS, " _____ " within DOSAGE AND ADMINISTRATION, and " _____ " within HOW SUPPLIED. Additionally, in the carton and foil pouch labeling, the container is referred to as " _____ ". To help minimize confusion, one term should be used consistently throughout the labeling when referring to the container.

B. FOIL POUCH LABELING

1. See General Comments A-1 and A-3 through A-5.
2. Revise the statement ' _____ ' to read "Usual Dosage: See package insert for dosage information." We refer you to 21 CFR 201.55 for guidance. b(4)
3. Relocate the "Contents: ..." statement away from the product strength and place in the bottom section of the panel.
4. DMETS acknowledges that the foil pouch submitted to the Agency is clinical trial material and not reflective of the pouch that will actually be used in the marketplace. However, we note that the labeling is difficult to read as a result of the black font on foil and should be revised before introduction into the marketplace (see Figure 6 below). A matte finish foil should be utilized or a white adhesive label, containing the required statements in black font, should be applied to the foil as an alternate solution. Alternatively, redesign the pouch so that the labeling is printed on a colored background which maximizes the contrast between text and background.



Figure 6. Cotraxal pouch labeling utilizing black font on foil background.

5. There are references to ' _____ '. DMETS is unsure as to whether the " _____ " portion of this statement is directing the patient/health care provider to the PRECAUTIONS (Information for Patients) section heading or to a separate patient information leaflet. If this reference is to the PRECAUTIONS section heading, delete the portion of the statement which reads ' _____ '. If this reference pertains to a separate patient information leaflet, the statement should be revised to reflect the type of patient information being referenced (i.e., a patient information leaflet). Additionally, we note that if the sponsor is referencing a separate patient information leaflet, such labeling was not submitted for review and comment. b(4)

C. CARTON LABELING

b(4)

D. INSERT LABELING

1. See General Comments A-3 and A-5.
2. Delete the use of trailing zeros and "µg" throughout the insert labeling. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "... to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." Otherwise, if the decimal point is not readily apparent, the potential for a ten-fold dosing error exists. Similarly, post-marketing experience has demonstrated that "µg" (microgram) and "mg" (milligram) may be confused. We further note that the use of trailing zeros and "µg" are specifically listed as dangerous abbreviations, acronyms, or symbols in the 2006 National Patient Safety Goals of The Joint Commission for Accreditation of Hospitals (JCAHO). Lastly, safety groups, such as the Institute for Safe Medication Practices (ISMP), also list trailing zeros and "µg" on their dangerous abbreviations and dose designations list.

3. PRECAUTIONS (Information for Patients)

- a. Include the following statements, _____

- b. In accordance with 21 CFR 201.57(f)(2), reprint the _____ subsection at the end of the package insert.

b(4)

4. DOSAGE AND ADMINISTRATION

- a. _____
- b. Define twice daily (e.g., "...the affected ear twice daily [about 12 hours apart, for example 8 AM and 8 PM] for seven days").

b(4)

5. HOW SUPPLIED

The statement "

the statement to read "...0.25 mL".

Revise

b(4)

Appendix A. DMETS prescription study results for Cetraxal®

Inpatient	Outpatient	Voice
Ceiaxal	Ataraxal	Atraxal
Cetianal	Atraxal	Cetiaval
Cetianal	Atraxal	Cetraxil
Cetianal	Atraxal	Cetraxil
Cetianal	Atraxal	Citraxal
Cetiaryl	Atraxal	Citraxal
Cetiaval	Atraxal	Citraxel
Cetiaval	Atraxal	Citraxel
Cetiaval	Atraxal	Citraxol
Cetiaval	Atraxal	Citraxol
Cetiaval	Cetraxal	Cytraxel
Cetiaval	Cetraxal	Fletrexal
Cetiaval	cetraxal	fortracksil
Cetiaval	Cetraxal	Protraxil
Cetiaxal	Cetraxal	Satraxil
Cetiaxal	Cetraxal	Satraxil
Cetiaxal	Cetraxal	Sotraxil
Cetiaxal	Cetraxal	Zotraxodol
Cetiaxal	Cetraxal	zytraxal
Cetiaxol	Cetraxal	
Cetranal	Cetraxal	
Cetranal	cetraxal	
Cetraval	Cetraxal	
Cetraval	Cetraxal	
Cetraxal	Cetraxal	
Cetraxal	Cetroxal	

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/s/

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