CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-157

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22, Mailstop 4447)

DATE RECEIVED: May 1, 2007 **DATE OF DOCUMENT:** March 27, 2007	**DESIRED COMPLETION DATE:** July 1, 2007 **PDUFA DATE:** January 28, 2008	**OSE REVIEW #:** 2007-984

TO: Badrul Chowdhury, MD
Director, Division of Pulmonary and Allergy Products
HFD-570

THROUGH: Linda Y. Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: **Xyzal**
(Levocetirizine Dihydrochloride) Oral Solution
0.5 mg/mL

NDA: **22-157**

SPONSOR: UCB, Inc.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Xyzal. DMETS notes that the application for "Xyzal" tablets was approved on May 25, 2007. Hence, in this review, we focused on the extension of the dosage form (i.e., oral solution) to see if the addition of a new dosage formulation could potentially create or increase the potential for confusion within the Xyzal product line in addition to creating potential confusion between the oral solution and other currrently marketed drug product names. Overall, we continue to have no objections to the name, Xyzal, and it does not appear that the addition of this new dosage form would increase the potential for confusion. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Xyzal, acceptable from a promotional perspective.

Please copy DMETS on any correspondence to the sponsor pertaining to this review. If you have questions or need clarification, please contact Darrell Jenkins, OSE Project Manager, at 301-796-0558.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
White Oak Bldg #22, Mailstop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: May 23, 2007

NDA #: 22-157

NAME OF DRUG: Xyzal
(Levocetirizine Dihydrochloride) Oral Solution
0.5 mg/mL

NDA HOLDER: UCB, Inc.

I. INTRODUCTION:

This review was written in response to a request from the Division of Pulmonary and Allergy Products (HFD-570), for assessment of the proposed proprietary name, Xyzal, regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

DMETS notes that the application for "Xyzal" tablets (NDA 22-064) was approved on May 25, 2007. Hence, in this review, we focused on the extension of the dosage form (i.e., oral solution) to see if the addition of a new dosage formulation could potentially create or increase the potential for confusion within the Xyzal product line in addition to creating potential confusion between the oral solution and other currrently marketed drug product names.

PRODUCT INFORMATION

Xyzal is currently available as a 5 mg tablet indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria. Xyzal oral solution is an extension to the current product line of Xyzal that consists of Xyzal 5 mg tablets. The oral solution has the same indications and recommended dosage as the tablets. Xyzal oral solution will be available in a 0.5 mg/mL (2.5 mg/5 mL) strength and supplied in cartons containing a glass (b) (4) bottle, each containing 5 ounces.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Xyzal to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. Prescription studies were not repeated for this third review. Following completion of these initial steps, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Xyzal. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Xyzal, acceptable from a promotional perspective.

2. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Xyzal. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

[1] MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)
[5] WWW location http://www.uspto.gov/tmdb/index html.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Xyzal	Levocetirizine dihydrochloride Tablets: 5 mg Oral solution: 0.5 mg/mL (2.5 mg/5 mL)	Seasonal allergic rhinitis, perennial allergic rhinitis, and uncomplicated skin manifestations of chronic idiopathic urticaria: *12 years of age and older*: 5 mg (10 mL) once daily in the evening. *Children 6 to 11 years of age*: 2.5 mg (5 mL) once daily in the evening.	NA
Kytril	Granisetron hydrochloride Tablets: 1 mg Oral solution: 0.2 mg/mL (1 mg/5 mL) Injection: 0.1 mg/mL and 1 mg/mL (Kytril oral solution has been discontinued; existing supplies are being depleted.)	Prevention of nausea and vomiting associated with emetogenic chemotherapy or radiation: *Oral*: 2 mg once daily or 1 mg twice daily while on chemotherapy; 2 mg within 1 hour of radiation. Prevention of nausea and vomiting associated with emetogenic chemotherapy; postoperative nausea and vomiting: *Injection*: 10 mcg/kg intravenously 30 minutes prior to chemotherapy; 1 mg intravenously before induction of anesthesia or immediately before reversal of anesthesia.	LA
Cefzil	Cefprozil Tablets: 250 mg and 500 mg Oral suspension: 125 mg/5 mL and 250 mg/5 mL	Infections caused by susceptible organisms in the following conditions: pharyngitis, otitis media, acute sinusitis, bronchitis, skin and skin structure infections: 500 mg once daily; 250 mg every 12 hours; or 500 mg every 12 hours depending on the condition being treated. Duration of therapy is 10 days.	LA
Eryzole	Erythromycin ethylsuccinate and sulfisoxazole Oral suspension 200 mg/600 mg per 5 ml	Acute otitis media: 50 mg (erythromycin)/150 mg (sulfisoxazole) per kg/day given in equally divided doses four times per day for 10 days.	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. SAFETY EVALUATOR RISK ASSESSMENT

DMETS notes that the application for "Xyzal" tablets was approved on May 25, 2007. Thus, this application for Xyzal oral solution provides for an addition to the Xyzal product line. Hence, in this review, we focused on the extension of the dosage form (i.e., oral solution) to see if the addition of a new dosage formulation could potentially create or increase the potential for confusion within the Xyzal product line in addition to creating potential confusion between the oral solution and other currrently marketed drug product names.

In reviewing the proprietary name, "Xyzal" oral solution, three names were identified as having a similar appearance or sound to Xyzal. These include: Kytril, Cefzil, and Eryzole.

Since Xyzal was approved in May, a search of the FDA *Adverse Event Reporting System* (AERS) was conducted to see if there have been reports of name confusion with Xyzal. AERS was searched using the MedDRA High Level Group Term "Medication Error" and the Preferred

Term “Pharmaceutical Product Complaint” and the drug names “Xyzal”, “levocetirizine”, and “levocetirizine dihydrochloride”. Using this strategy, there were no reports retrieved concerning Xyzal (n=0).

Upon further analysis of the names Cefzil and Eryzole it was determined that these names would not be reviewed further because they lack convincing look-alike/sound-alike similarities with Xyzal in addition to having differentiating product characteristics such as the product strength, indication of use, and/or frequency of administration. Additionally, there have been no reports of confusion between these names and Xyzal.

In review of the visual similarity of Kytril to Xyzal, we have the following comments:

Kytril (granisetron hydrochloride) is indicated for the prevention of nausea and vomiting associated with chemotherapy, radiation therapy, and postoperative nausea and vomiting. Kytril is available as oral tablets (1 mg), oral solution (0.2 mg/mL), and injection (0.1 mg/mL and 1 mg/mL). The recommended oral dose is 2 mg once daily or 1 mg twice daily while on chemotherapy or 2 mg within 1 hour of radiation. The recommended intravenous dose is 10 mcg/kg thirty minutes prior to chemotherapy or 1 mg intravenously before induction of anesthesia or immediately before reversal of anesthesia.

Kytril may look similar to Xyzal because the letters “Ky” and “Xy” may look similar when scripted. Additionally, the letters “t” and “z” may look similar when the letter “z” is crossed and written without a downstroke. Furthermore, both names end with the letter “l” which contributes to the look-alike similarities between the names. However, Kytril contains six letters which includes the letters “r” and “i” which may help to differentiate it from Xyzal which contains five letters. Additionally, the letter “z” in Xyzal has the same location as the letter “t” in Kytril. Therefore, when the letter “z” is scripted with a downstroke, the names are more easily differentiated because of the two sequential downstroke letters (i.e., “y” and “z”) in Xyzal.

Kytril and Xyzal have some overlapping product characteristics such as route of administration (oral), dosage form (oral solution and tablets) and frequency of administration (once daily) which may contribute to confusion between the names. For example, a prescription for Kytril or Xyzal oral solution could be written without a strength/concentration and with only the number of teaspoons or milliters (mL) to be taken since the oral solutions are available in one strength (e.g., “Xyzal oral solution, Take one teaspoonful once daily”). However, Kytril and Xyzal differ in indication of use (prevention of nausea and vomiting vs. seasonal/perennial allergic rhinitis and idiopathic urticaria), dose (1 mg, 2 mg, or 10 mcg/kg vs. 2.5 mg or 5 mg), and strength (1 mg tablet, 0.2 mg/mL oral solution, 0.1 mg/mL injection and 1 mg/mL injection vs. 5 mg tablet and 0.5 mg/mL oral solution) which may help to differentiate the names. Furthermore, a prescription for Kytril may give specific instructions to take “prior to chemotherapy” or “radiation therapy” whereas a prescription for Xyzal may state to take “once daily” or “as directed”. DMETS also notes that the manufacture of Kytril oral solution has been discontinued and existing supplies are being depleted.[7] Although there are some orthographic similarities between this name pair, the

[7] Kytril (granisetron hydrochloride) Oral Solution (NDA 21-238); Annual Report (May 1, 2006 to April 30, 2007).

different product characteristics will minimize the potential to confuse the names. Additionally, DMETS has not, thus far, identified any medication error reports involving this name pair.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Xyzal oral solution, DMETS has focused on human factors and safety issues relating to possible medication errors. DMETS has identified the following areas of improvement which might minimize potential user error. Please note that our comments concerning the package insert (PI) labeling are based on our review of the revised PI submitted on July 31, 2007 (as requested by the Division).

A. GENERAL COMMENTS

1. (b) (4)

2. The established name is presented as "levocetirizine 2HCl". Using the number "2" as part of the established name may be confusing and misinterpreted by consumers and healthcare professionals. DMETS recommends that the established name be spelled out in its entirety (i.e., "levocetirizine dihydrochloride") in order to maintain clarity and avoid potential errors that may result from using a number as part of the established name designation.

3. Ensure that the established name is at least ½ the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

4. The recommended dose for this product is either 2.5 mg or 5 mg. This will require the administration of 5 mL or 10 mL. Thus, we request the statement of strength read "2.5 mg/5 mL (0.5 mg/mL)" in order to improve clarity since the dose may be prescribed in terms of the number of milliliters or teaspoonsful to be administered. This will help to minimize the potential for dosage calculation errors. See the example below for the recommended presentation of the statement of strength.

2.5 mg/5 mL (0.5 mg/mL)

5. Increase the size of the statement of strength and relocate the statement of dosage form (oral solution) so that it is positioned adjacent to or below the established name in order to increase the prominence of the statement of strength. Additionally, ensure that the established name and dosage form are printed in the same font type, size, boldness, etc. Please see the example below for positioning of the wording.

Xyzal (levocetirizine dihydrochloride) oral solution 2.5 mg/5 mL (0.5 mg/mL)

B. CONTAINER

1. See General Comments.

2. If this is a "unit of use" bottle and dispensed on an outpatient basis, ensure that it has a Child Resistant Closure in accordance with the Poison Prevention Act.

Container Label

C. CONTAINER (PROFESSIONAL SAMPLE)

1. See General Comments and B-2.

2. Relocate the statement "Professional Sample-Not for Sale" to the principal display panel.

D. CARTON LABELING (TRADE AND PROFESSIONAL SAMPLE)

See General Comments.

E. INSERT LABELING

1. The established name as presented on the container labels and carton labeling (levocetirizine 2HCl) is inconsistent with that printed in the package insert labeling (levocetirizine dihydrochloride). Using the number "2" as part of the established name may be confusing and misinterpreted by consumers and healthcare professionals. DMETS recommends that the established name be spelled out in its entirety (i.e., "levocetirizine dihydrochloride") in order to maintain clarity and avoid potential errors that may result from using a number as part of the established name designation. Please ensure that the established name used is consistent throughout all of the product labels and labeling.

2. In the Adverse Reactions section (6.1) and other sections of the PI, DMETS notes that the Xyzal doses are printed in sequence as "XYZAL 2.5, 5, or 10 mg". DMETS recommends that the numerical dose (i.e. 2.5, 5, etc.) be followed by the corresponding unit of measure (i.e., "mg") in order to improve clarity. For example: "XYZAL 2.5 mg, 5 mg, or 10 mg".

3. The "manufactured by" information printed on the carton and container labels does not correspond with that printed in the PI. Please ensure that this information is consistent throughout all the product labels and labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Loretta Holmes
8/24/2007 02:05:07 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
8/24/2007 03:56:24 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/24/2007 04:22:39 PM
DRUG SAFETY OFFICE REVIEWER