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*APPLICATION NUMBER:*

**22-157**

**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: January 17, 2008

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From: Loretta Holmes, BSN, PharmD, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

Subject: DMETS Label and Labeling Review

Drug Name(s): Xyzal (Levocetirizine Dihydrochloride) Oral Solution  
2.5 mg/5 mL (0.5 mg/mL)

Application Type/Number: NDA 22-157

Applicant/sponsor: UCB, Inc.

OSE RCM #: 2007-2514

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## EXECUTIVE SUMMARY

In our analysis of the revised container labels, carton and insert labeling for Xyzal oral solution, we noted several areas of concern with respect to the presentation of information on the labels/labeling. The statement of strength, as currently presented, may introduce unnecessary confusion due to the use of two strength designations. Additionally, certain less important information appears more prominent on the carton label and/or container labeling than is necessary which detracts from other important information that is present. These concerns need to be addressed prior to approval in order to minimize the potential for medication errors and improve the readability and user friendliness of the information.

## 1 BACKGROUND

### 1.1 INTRODUCTION

This review is written in response to a December 12, 2007 request from the Division of Pulmonary and Allergy Products (HFD-570) for a re-review of the tradename, labels and labeling of Xyzal oral solution. DMETS notes that Xyzal (tablet formulation) was approved on May 25, 2007. Please refer to OSE Review 2007-984, dated August 24, 2007, in which DMETS had no objections to the use of the name "Xyzal" for this dosage form of the product. Hence, this review focused on the revised Xyzal oral solution labels and labeling.

### 1.2 REGULATORY HISTORY

Xyzal (tablet formulation) was approved on May 25, 2007.

### 1.3 PRODUCT LABELING

Xyzal is a histamine H<sub>1</sub>-receptor antagonist indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis and the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older. The recommended dosages are as follows (see Table 1, below). For adults and children 12 years of age and older with impaired renal function, the recommended dosages are as follows (see Table 2, page 2). Xyzal oral solution will be available in a 2.5 mg/5 mL (0.5 mg/mL) strength and supplied in 5 oz. glass bottles.

Table 1. Xyzal Oral Solution Dosage and Administration

Age	Recommended Dose
Adults and children 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

Table 2. Xyzal Oral Solution Dosage and Administration  
(Renal Impairment, 12 years of age and older)

Creatinine Clearance	Recommended Dose
50-80 mL/min	2.5 mg (5 mL) once daily
30-50 mL/min	2.5 mg (5 mL) once every other day
10-30 mL/min	2.5 mg (5 mL) twice weekly (administered once every 3-4 days)
Less than 10 mL/min (end-stage renal disease patients) and patients undergoing hemodialysis	Should not receive Xyzal

## 2 METHODS AND MATERIALS

### 2.1 AERS SELECTION OF CASES

Since Xyzal is a currently marketed product, DMETS conducted a search of the FDA *Adverse Event Reporting System* (AERS) for medication errors involving Xyzal since errors associated with the use of the currently available tablets should be taken into consideration when reviewing the labels and labeling for the oral solution. DMETS searched AERS using the MedDRA High Level Group Term "Medication Errors" and the Preferred Term "Pharmaceutical Product Complaint", the tradename "Xyzal" and active ingredients "levocetirizine" and "levocetirizine dihydrochloride" for medication error cases dated through December 21, 2007.

### 2.2 PROPOSED LABEL/LABELING

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on the configuration) interact with the pharmaceutical product. The carton and container labels communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration date, 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.<sup>1</sup>

Because DMETS staff analyze reported misuse of drugs, DMETS staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMETS uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling and provide recommendations that aim at reducing the risk of medication errors.

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<sup>1</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p 275.

For this product, the sponsor submitted on November 13, 2007 the following labels and labeling for DMETS review (see Appendix A):

- Container Label: Professional Sample (15 mL) and commercial (148 mL)
- Carton Labeling: Professional Sample (15 mL) and commercial (148 mL)
- Package Insert Labeling

### **3 RESULTS**

#### **3.1 AERS SELECTION OF CASES**

The AERS database search did not retrieve any cases that were pertinent to this review.

#### **3.2 PROPOSED LABELS/LABELING**

##### **3.2.1 Container Labels**

The milligram per milliter strength designation (“0.5 mg/mL”) is present but does not correspond to the lowest recommended dose in the package insert labeling (i.e., 2.5 mg which is equivalent to 5 mL).

The “UCB” logo on the commercial container label appears more prominent on the label than the proprietary name, established name, and strength.

The net quantity statement on the commercial label is printed in bold lettering.

##### **3.2.2 Carton Labeling**

The milligram per milliter strength designation (“0.5 mg/mL”) is present but does not correspond to the lowest recommended dose in the package insert labeling (i.e., 2.5 mg which is equivalent to 5 mL).

In the professional sample carton labeling, the “Professional Sample” statement is positioned too close to the proprietary name.

##### **3.2.3 Package Insert Labeling**

The milligram per milliter strength designation (“0.5 mg/mL”) is present but does not correspond to the lowest recommended dose in the package insert labeling (i.e., 2.5 mg which is equivalent to 5 mL).

### **4 DISCUSSION**

In our review of the revised container labels, carton and insert labeling, we noted that the presentation of the statement of strength is not optimal and may be confusing. DMETS acknowledges that in our previous labeling review (OSE Review 2007-984, dated August 24, 2007) we recommended the addition of “2.5 mg/5 mL” to the “0.5 mg/mL” strength designation that was already on the labels/labeling. However, we now realize that because 2.5 mg is the lowest recommended dose, the “0.5 mg/mL” designation is unnecessary and, in fact, may cause undue confusion.

We also noted that the “Professional Sample” statement on the professional sample carton is positioned too close to the proprietary name, established name, and strength and is therefore distracting in this location. The “Professional Sample” statement can be relocated so that it does

not detract from this important product information. This will also improve the readability of the carton labeling.

Additionally, the "UCB" logo on the commercial container label appears more prominent on the label than the proprietary name, established name, and strength which interferes with the readability of this information. Modifying the size of the logo to decrease its prominence will enhance the readability of important product identifying information. Finally, the net quantity statement on the trade container label is printed in bold which gives it more prominence than is necessary.

## **5 CONCLUSIONS AND RECOMMENDATIONS**

As proposed, the revised container labels and carton labeling are designed in such a manner that the readability and presentation of certain information is not optimal. However, minor changes can be made in order to make the labels/labeling more user friendly. In review of the container labels, carton and insert labeling, DMETS has applied principles of human factors and evaluated the labels and labeling using Failure Mode and Effects Analysis (FMEA). Our analysis identified the following areas of needed improvement.

### **5.1 CONTAINER LABELS**

- 5.1.1** Delete the "0.5 mg/mL" portion of the strength designation so that the statement of strength states "2.5 mg/5 mL" only.
- 5.1.2** Decrease the size of the "UCB" logo on the commercial container label.

### **5.2 CARTON LABELING**

- 5.2.1** Delete the "0.5 mg/mL" portion of the strength designation so that the statement of strength states "2.5 mg/5 mL" only.
- 5.2.2** Relocate the "Professional Sample" statement so that it is not positioned next to the product identifier information (proprietary name, established name, and strength).

### **5.3 PACKAGE INSERT LABELING**

- 5.3.1** Delete the "0.5 mg/mL" portion of the strength designation so that the statement of strength states "2.5 mg/5 mL" only.

DMETS would appreciate feedback on the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence to the sponsor pertaining to this issue. If you have further questions or need clarifications, please contact Cheryl Wiseman, OSE Project Manager, at 301-796-0567.

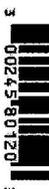
## 6 REFERENCES

### Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports of approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from healthcare professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

APPENDICES

Appendix A. Xyzal Oral Solution Container Labels

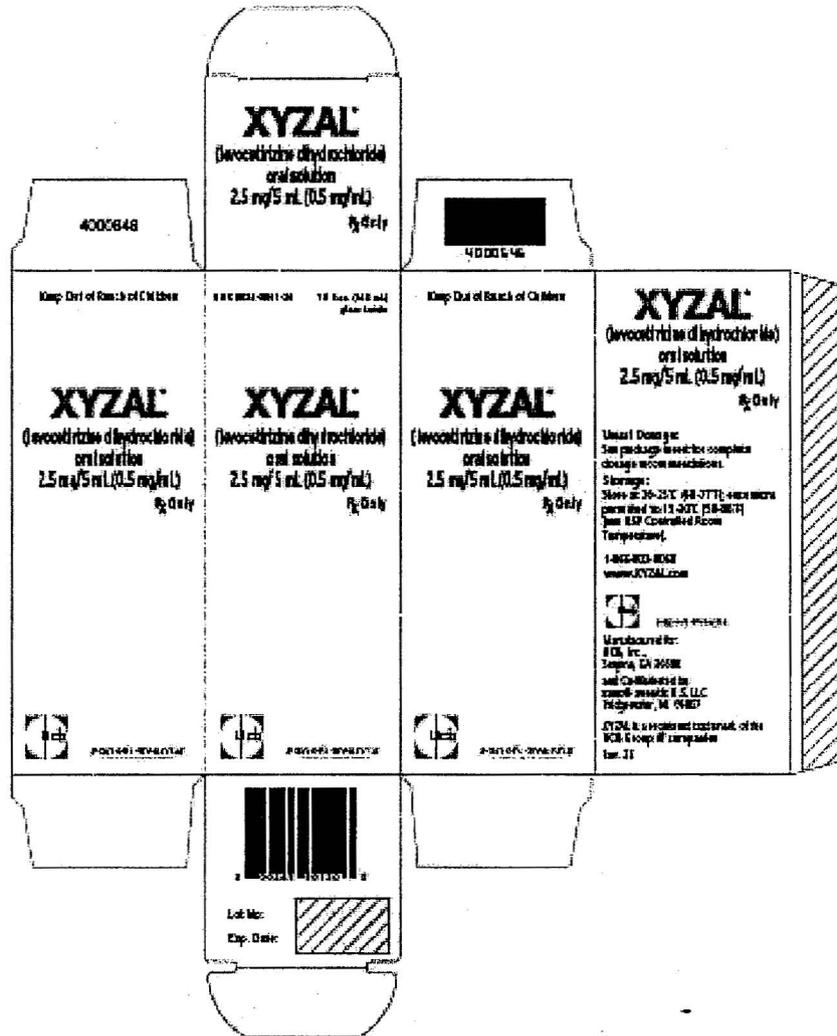
 00245801201	<b>Usual Dosage:</b> See package insert for complete dosage recommendations.	<b>NDC 0024-5801-20 5 oz. (148 mL)</b>	<b>Manufactured for:</b> UCB, Inc., Smyrna, GA 30080 and
	<b>Storage:</b> Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep Out of Reach of Children.	<b>XYZAL®</b> <b>(levocetirizine dihydrochloride)</b> <b>oral solution</b> <b>2.5 mg/5 mL (0.5 mg/mL)</b>	<b>Co-marketed by:</b> sanofi-aventis U.S. LLC Bridgewater, NJ 08807
		<b>Rx Only</b>	<b>1-866-822-0068</b>
	<b>sanofi-aventis</b>		<b>Rev. 2E</b>

Commercial Container Label (not actual size)



Professional Sample Container Label (not actual size)

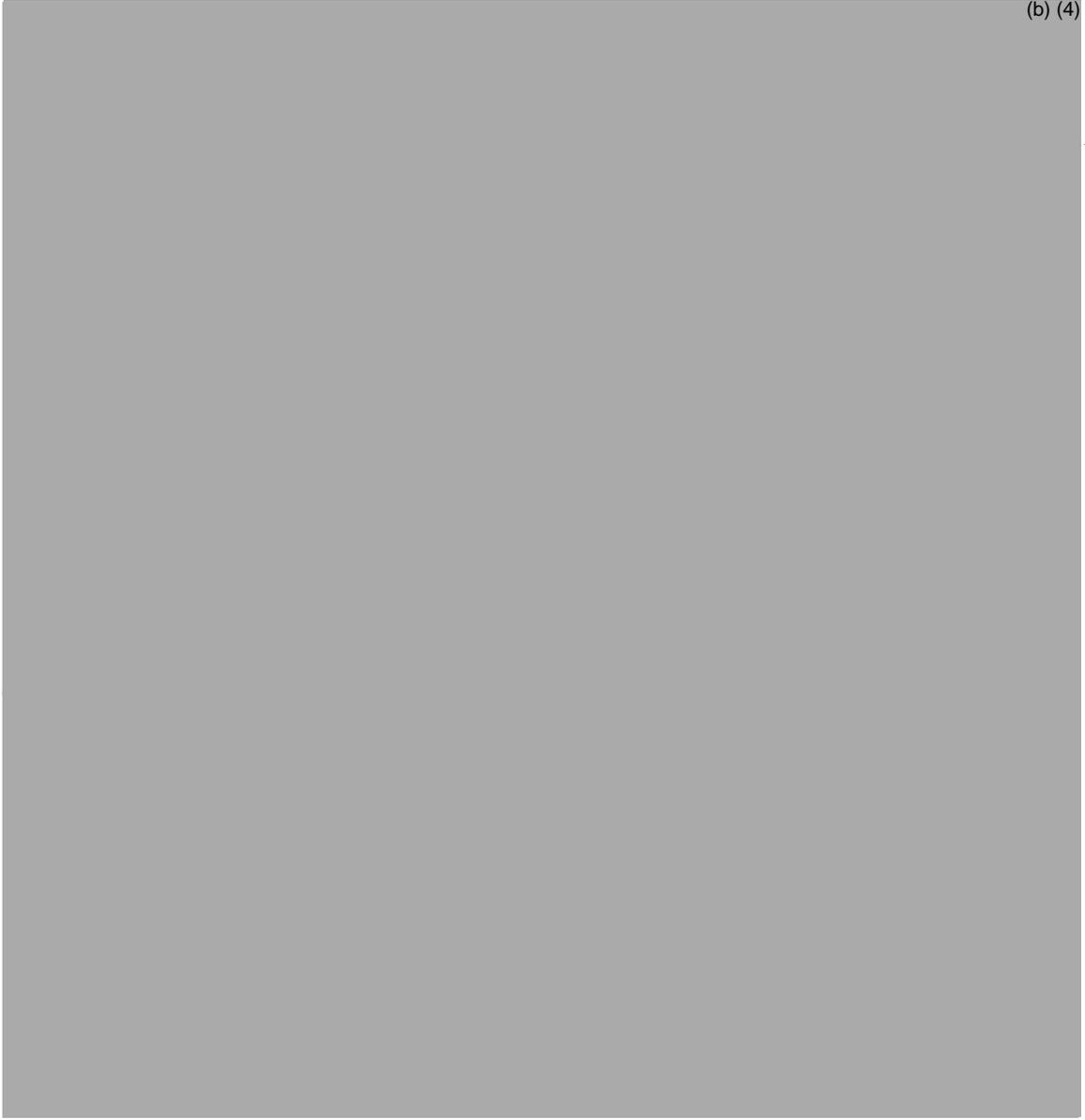
Appendix B. Xyzal Oral Solution Carton Labeling



Commercial Carton Labeling (not actual size)

Appendix B. Xyzal Oral Solution Carton Labeling (cont'd)

(b) (4)



Professional Sample Carton Labeling (not actual size)

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/s/  
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Linda Kim-Jung  
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**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

## Memorandum

**Date:** May 3, 2007

**To:** Lori Garcia, RPh – Regulatory Project Manager  
Division of Pulmonary and Allergy Products (DPAP)

**From:** Michelle Safarik, PA-C – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Subject:** NDA 22-157  
DDMAC labeling comments for Xyzal (levocetirizine  
dihydrochloride) Tablets and Oral Solution

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Per your consult request dated April 30, 2007, DDMAC has reviewed the proposed product labeling (PI) and proposed carton and container labeling for Xyzal (levocetirizine dihydrochloride) Tablets and Oral Solution (Xyzal).

DDMAC acknowledges that the draft Physician Labeling Rule (PLR) PI submitted in the 120-day safety update for NDA 22-064 (Xyzal Tablets) is the basis for this proposed PI, which has been modified from that submitted in NDA 22-064 to reflect the addition of the oral solution dosage form (NDA 22-157). DDMAC also acknowledges that the sponsor will submit a revised proposed PI to NDA 22-157 subsequent to the availability of the final approved PI for NDA 22-064.

Reference is made to DDMAC labeling consult responses dated March 8, 2007, and March 13, 2007, providing comments on the proposed PI and proposed carton and container labeling for Xyzal Tablets (3/8/07) and on the revised proposed carton and container labeling for Xyzal Tablets (3/13/07). We offer the following comments.

### Highlights

#### Indications and Usage

1. Is it appropriate to include the limitation to the three indications that use is intended for patients  $\geq 6$  years of age?
2. "...due to allergens such as (b) (4) ...due to (b) (4)

It is DDMAC's understanding that DPAP currently discourages parsing out specific allergens in labeling and promotional materials for drugs with seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) indications. Therefore, unless the sponsor has substantial evidence to support claims of treatment for specific allergens, we recommend deleting the above phrases.

### Adverse Reactions

1. While the incidence rate for each adverse reaction need not be included, we recommend that the cut-off rate ( $\geq 2\%$ ) be included for consistency with the Adverse Reactions section of the proposed PI.

### PI

#### Indications and Usage

(Please see comments under Highlights – Indications and Usage).

1. (b) (4)

The above claims discuss efficacy findings, and thus should be removed from the Indications and Usage section of the proposed PI. In addition, they are repetitive with the information provided in the Clinical Studies section of the proposed PI, and we recommend deletion.

#### Warnings and Precautions

1. (b) (4)

Were the comparative clinical trials appropriately designed to constitute substantial evidence to support such a promotional safety claim? If not, we recommend deletion, as this claim is contradictory to the risk information that follows, has major promotional implications, and minimizes the risks of the drug. Please note that the risk information in the remainder of the paragraph does not mitigate the above claim's misleading nature.

## Adverse Reactions

1. "Serious adverse events were observed (b) (4) in 15 of 4067 unique subjects...The causal relationship of these (b) (4) serious adverse events..." (emphasis added).

We recommend deletion of the words (b) (4) " and (b) (4) since they are promotional in tone (minimize the risks of the drug) and context is provided.

2. We recommend American English spellings for "dyspnoea" (dyspnea) and "oedema" (edema).

## Description

1. "XYZAL 5 mg tablets are formulated as immediate release...XYZAL 0.5 mg/mL oral solution is formulated as an immediate release..." (emphasis added).

Is it accurate to state that Xyzal is "immediate release," particularly since the drug is dosed only once daily? If not, we recommend deletion.

## Clinical Pharmacology

1. (b) (4)

Dr. Lydia Gilbert-McClain previously commented at the Xyzal wrap-up meeting on March 26, 2007, that the second statement above is promotional in tone. DDMAC concurs, as these are implied comparative claims. While these statements may be accurate, they may be used in promotional materials to make unsubstantiated superiority claims. Therefore, unless this information is absolutely crucial for the prescriber in clinical practice, we recommend deletion.

2. "... (b) (4) inhibited the skin wheal and flare...caused a (b) (4) inhibition of the histamine induced wheal and flare... (b) (4) inhibited the wheal and flare..." (emphasis added).

Are (b) (4) and (b) (4) universally accepted and understood terms in clinical practice? If not, we recommend either adding context or deleting.

3. "...levocetirizine 5 mg was found to have a (b) (4) onset of action within 30 minutes of oral intake and a (b) (4) duration of action greater than or equal to 29 hours" (emphasis added).

"Short" and "long" are promotional in tone; we recommend deletion since context is provided for both terms. In addition, we recommend providing context for "greater than" 29 hours.

4. "...and the activity persisted for at least 24 hours" (emphasis added).

We recommend providing context for "at least" 24 hours.

5. "Levocetirizine is (b) (4) and extensively absorbed following oral administration" (emphasis added).

"Rapidly" is promotional in tone; we recommend deletion since context is provided in the next sentence (i.e., 0.9 hour after administration of the oral tablet).

6. "Levocetirizine at concentrations well above C<sub>max</sub> level achieved within the therapeutic dose ranges is not an inhibitor of CYP isoenzymes..." (emphasis added).

We recommend providing context for "well above" C<sub>max</sub> level.

### Clinical Studies

1. "...compared the effects of XYZAL with placebo and/or active compounds in adult patients with perennial or seasonal allergic rhinitis" (emphasis added).

Is it unclear what "active compounds" refers to – are they active comparator drugs, the house dust mites and grass pollen discussed later in the paragraph, or something else? We recommend specifying what these "active compounds" are for clarity.

2. (b) (4)

(b) (4)

(b) (4)

If not, we recommend deletion.

3. "The efficacy results showed that all XYZAL doses were statistically (b) (4) to placebo in improving symptoms of chronic idiopathic urticaria..." (emphasis added).

(b) (4) is promotional in tone; we recommend revising (b) (4) to "significant."

**Carton and Container Labeling**

We have reviewed the proposed carton and container labeling and have no comments at this time.

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