

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-411**

**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: July 6, 2009

To: Thomas Laughren, MD, Director  
Division of Psychiatry Products

Through: Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Kellie Taylor, PharmD, MPH, Team Leader  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Oleptro (Trazodone HCl) Extended-release Tablets  
150 mg and 300 mg

Application Type/Number: NDA# 22-411

Applicant: Labopharm

OSE RCM #: 2009-341

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## 1 METHODS AND MATERIALS

This review was written in response to a request from the Division of Psychiatry Products to review the Applicant's revised container labels, blister and carton labeling pursuant to recommendations made in OSE Review 2008-1551 dated May 1, 2009.

The Division of Medication Error Prevention and Analysis (DMEPA) used principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the revised container labels, blister and carton labeling submitted on June 10, 2009 (see Appendices A and B for images).

## 2 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling can be improved to minimize the potential for medication errors. DMEPA previously provided recommendations on the labels and labeling in OSE Review #2008-1333 dated December 19, 2009. It does not appear that the previous Applicant implemented these recommendations.

Section 2.2 *Comments to the Applicant* contains our recommendations for the container label, carton labeling, and insert labeling. We request that the recommendations in Section 2.1 be communicated to the Applicant prior to approval of the labeling supplement.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Janet Andersen, OSE Project Manager, at 301-796-0675.

### 2.1 COMMENTS TO THE APPLICANT

#### 2.1.1 General Comments

In order to comply with 21 CFR 208.24, carton labeling and container labels must conspicuously bear statements indicating that a Medication Guide must be dispensed. Appropriate wording would include: "Dispense the enclosed Medication Guide to each patient" or "Dispense accompanying Medication Guide to each patient"

Please revise the labels and labeling accordingly, and resubmit with review. Please also indicate how the Medication Guide will be provided (e.g. attached to the bottle, enclosed in the carton) and ensure that sufficient numbers are available for distribution to each patient prescribed Olepto in accordance with 21 CFR 208.24.

#### 2.1.2 Container Labels and Carton Labeling

1. The 150 mg and 300 mg strengths are similar in appearance. More prominent differentiation of the 150 mg or 300 mg labels may help to ensure that the products have adequate visual differentiation from one another.
2. The statement "Bisectable tablets- Do not crush or chew" is confusing. Please clarify the wording to convey that the tablets may be split, but not crushed or chewed. Alternatively, revise the statement to read "Do not crush or chew".
3. Revise the fonts of the established name so that the established name is at least one half as large as the letters comprising the proprietary name and ensure that the established name has a prominence commensurate with the prominence of the proprietary name taking into account all pertinent factors, including typography,

layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

### **2.1.3 *Blister Labels***

Revise the fonts of the established name so that the established name is at least one half as large as the letters comprising the proprietary name and ensure that the established name has a prominence commensurate with the prominence of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

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/s/

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Kellie Taylor  
7/8/2009 03:36:47 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
7/8/2009 05:42:49 PM  
DRUG SAFETY OFFICE REVIEWER



**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: July 2, 2009

To: Thomas Laughren, M.D. Division Director  
**Division of Psychiatry Products**

Through: Jodi Duckhorn, MA, Team Leader  
**Division of Risk Management**

From: LaShawn Griffiths, MSHS-PH, BSN, RN  
Patient Product Information Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): Oleptro (trazodone hydrochloride)

Application Type/Number: NDA 22-411

Applicant/sponsor: Labopharm Europe Limited

OSE RCM #: 2008-1552

## **1 INTRODUCTION**

Labopharm Europe Limited submitted a New Drug Application (NDA 22-411) for Oleptro (trazodone hydrochloride) on September 18, 2008. The submission includes proposed Professional Information (PI) in PLR format, and Patient Labeling Information (Medication Guide). Oleptro is indicated for the treatment of acute major depressive disorder in adults.

## **2 MATERIAL REVIEWED**

- Oleptro Medication Guide (MG) submitted September 18, 2008
- Oleptro Prescribing Information (PI) submitted September 18, 2008 and revised by the Review Division throughout the current review cycle

## **3 DISCUSSION**

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

Content and formatting revisions are made to ensure that the information is legible, clear, and patient-friendly. Patient Information that is well designed and clearly worded can help to maximize patient use and understanding of important safety information that is presented.

The draft MG submitted by the Applicant has a Flesch Kinkaid grade level of 10.1, and a Flesch Reading Ease score of 47.6%. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). Our revised MG has a Flesch Kinkaid grade level of 8.9 and a Flesch Reading Ease score of 52.8%.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- removed unnecessary or redundant information
- ensured that the Medication Guide meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information more accessible for patients with low vision. We have

reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are **bolded, underlined and italicized**.

We are providing the review division a marked-up and clean copy of the revised MG.

All future relevant changes to the PI should also be reflected in the MG.

#### **4 CONCLUSIONS AND RECOMMENDATIONS**

1. The Applicant uses both the terms “doctor,” and “healthcare provider” in the proposed MG. We recommend that one term be used consistently throughout the MG. For this review we have used the term “healthcare provider”.
2. In the “What is Oleptro?” section the disease specific information was removed. The purpose of Patient Information is to enhance appropriate use and to provide important information to patients about medications. This is disease specific information that can be placed at the end of the MG after the “Ingredients” section or preferably be addressed with the patient separately from the product specific information.
3. The “Who should not take Oleptro?” section was removed because the “Who should not take” section is limited to contraindications, Oleptro has “no” contraindications to use.
4. In the “What should I tell my healthcare provider before taking Oleptro?” section (b) (4) was removed because it is not listed in the PI. If the Applicant wishes to include this in the MG it must first be added to the PI.
5. In the “What should I tell my healthcare provider before taking Oleptro?” section a list of medicines were added from the PI. We defer to the RD on deciding if the long list of medicines need to be included, or if a general statement to “tell your healthcare provider about all the medicines you take” will be enough.
6. In the section “What should I tell my healthcare provider before taking Oleptro?” 5.8 of the PI states “at least 14 days should be allowed after stopping Oleptro before starting an MAOI”. Therefore (b) (4) as the Applicant proposed was changed to 14 days.
7. In the “How should I take Oleptro?” section (b) (4) was removed because it is not listed in the PI. If the Applicant wishes to include this information in the MG it must first be added to the PI.
8. In the “How should I store Oleptro?” section (b) (4) was removed because it is not listed in the PI. For consistency if the Applicant wishes to add this information to the MG it must first be added to the PI.

Please let us know if you have any questions.

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/s/

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LaShawn Griffiths  
7/2/2009 03:51:26 PM  
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn  
7/2/2009 03:53:14 PM  
DRUG SAFETY OFFICE REVIEWER

# MEMORANDUM

**To:** William Bender  
Division of Psychiatry Products

**From:** Iris Masucci, PharmD, BCPS  
Division of Drug Marketing, Advertising, and Communications  
for the Study Endpoints and Label Development (SEALD) Team, OND

**Date:** June 26, 2009

**Re:** Comments on draft labeling for Oleptro (trazodone HCl) extended-release tablets  
NDA 22-411

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We have reviewed the proposed label for Oleptro (FDA version dated 6/24/09) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

Please see attached label for recommended changes.

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/s/

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Iris Masucci  
6/30/2009 02:55:31 PM  
DDMAC PROFESSIONAL REVIEWER

Laurie Burke  
7/6/2009 03:01:27 PM  
INTERDISCIPLINARY

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

**DATE:** May 20, 2009

**TO:** William Bender, Regulatory Project Manager  
Victor Crentsil/Gwenn Zornberg/Medical Officers  
Division of Psychiatry Products

**FROM:** Sharon K. Gershon  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

**THROUGH:** Tejashri Purohit-Sheth  
Branch Chief  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections.

**NDA:** 22-411

**APPLICANT:** Labopharm, Inc., Mundelem, IL

**DRUG:** Trazodone Contramid® OAD (trazodone HCl)

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** Unipolar Major Depressive Disorder

**CONSULTATION REQUEST DATE:** September 18, 2008

**DIVISION ACTION GOAL DATE:** July 1, 2009

**PDUFA DATE:** July 18, 2009

## I. BACKGROUND:

The sponsor seeks approval of Trazodone Contramid® OAD for the treatment of Unipolar Major Depressive Disorder (MDD). Study 04ACL3-001 is the only study submitted by the sponsor to support the efficacy claim for the proposed indication. Trazodone HCL is a triazolopyridine derivative and a serotonin-2 antagonist as well as a selective postsynaptic inhibitor of serotonin reuptake. Trazodone Contramid® OAD is the first extended-release formulation of trazodone HCL to be introduced to the US. An enrollment of 412 subjects occurred at 37 sites (30 U.S., 8 Canada).

The total study duration of the study was 11 weeks, with up to 3 weeks for screening and the washout of prohibited drugs, then 2 weeks of titration of drug or placebo and 6 weeks of treatment at the final titration dose level. The study had 4 different dosage levels -150 mg, 225 mg, 300 mg and 375 mg. Rescue medication for the treatment of MDD was not allowed. Subjects were discontinued if dose adjustment was not successful in treating intolerable symptoms or adverse events. Participants orally self-administered the study medication once daily at bedtime.

The primary efficacy endpoint was the change in total score of the Hamilton Depression Rating Scale (17-item scale) [HAMD-17] from baseline (the last measurement before the first dose at Visit 2) to the last visit. Secondary outcome measures included: a) HAMD – responders, remitters, depressed mood item; b) MADRS – change from baseline; c) CGI-1 and PCG-1 responders and score at last study visit; e) CGI-S: change from baseline; f) Quality of Sleep assessment; g) Discontinuations due to lack of efficacy; h) Safety parameters.

The sites below were selected for audit because they enrolled large numbers of study subjects. Exclusion of the data from Site 001 would have an appreciable impact on the p-value of primary efficacy endpoint.

The protocol inspected was: 04ACL3-001: “A Randomized, Double-Blind, Two-Arm Study Comparing the Efficacy and Safety of Trazodone Contramid® OAD and Placebo in the Treatment of Unipolar Major Depressive Disorder (MDD).”

## II. RESULTS (by Site):

Site #/Name of CI	Protocol #: and # of Subjects:	Inspection Date	Final Classification
Site 001 Guiseppe Mazza, MD Clinique Medicale Langelier, 6058 Jean-Talon Est, St-Leonard, QC,	04ACL3-001  40 subjects	02/23- 02/27/2009	VAI
Site 111 Steven J. Glass, MD CRI Worldwide, LLC	04ACL3-001	01/13 – 01/26/2009	NAI

130 White Horse Pike, Clementon, NJ 08021	26 subjects		
Site 106 John Carman, MD Carman Research 4015 S.Cobb Drive, Suite 245 Smyrna, GA 30080	04ACL3-001  14 subjects	02/09 – 02/12/2009	NAI
Site 120 Dennis J.Munjack, MD Southwestern Research, Inc. 435 North Bedford Drive, Suite 216, Beverly Hills, CA	04ACL3-001  20 subjects	01/05- 01/20/2009	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;  
EIR has not been received from the field and complete review of EIR is pending.**1. Guiseppe Mazza, Clinique Medicale Langelier, 6058 Jean-Talon Est, St-Leonard, QC,**

**What was inspected:** A total of 44 subjects were screened at Site 001, and 40 subjects were enrolled - 34 subjects completed the study. The inspection reviewed all 44 subject records with respect to primary efficacy endpoint and signed informed consent documents. The inspection conducted an in-depth review of study records for 24 subjects, with respect to eligibility criteria, SAEs/AEs, adherence to protocol, and test article accountability records.

**Observations:** For the 24 subjects, all met eligibility criteria. A total of 4 SAEs occurred, and the inspection found two that were not reported promptly to the sponsor, or the IRB (subjects 001029 and 001021). Subject 001029 had duodenal ulcer and gastritis that required hospitalization from (b) (6). The inspection reported that Dr. Mazza did not recognize the event to be an SAE, and thus did not report the event to either the IRB or the sponsor until December 9, 2008 (over 1 year later), when the study monitor performed an audit in preparation for the FDA inspection. A second SAE was for Subject 001021. This subject experienced two suicide attempts - one on (b) (6) that required an emergency room visit, and a 2<sup>nd</sup> attempt 6 days later on (b) (6). Dr. Mazza did not become aware of the first suicide attempt until (b) (6) and thus did not report it immediately. The subject's second attempt resulted in a hospitalization, and this event was reported promptly. Other observations noted were:

- i) telephone contacts (made to subjects between Visit 2 and Visit 3, Visit 3 and Visit 4, Visit 6 and Visit 7, and Visit 7 and Visit 8) did not identify the name or signature of the person who made the contact;
- ii) subject's study records were co-mingled with subject's clinic records;
- iii) site did not maintain a master inventory log that recorded the dates and amounts when test article was received. As drug shipments were received, the study coordinator entered shipment data electronically into the IVR system, and a fax confirmation of acceptable receipt was then obtained.
- iv) study drug was stored in a storage cabinet along with study drugs from 7 other studies. There appeared to be ample separation among the study drugs.
- v) the site re-dispensed study medication from prior blister cards to 4 subjects, during the study. The re-dispensing was reported due to the unavailability of blister cards designated for the subjects at the time of their scheduled site visits. The latter occurred because of the IVR system failure to adequately manage allocation of drug at this site, which resulted in delays of medication to the site. This item was not listed on the FDA-483.

A 3-observational item FDA-483 was issued to Dr. Mazza, concerning the above observations.

**Assessment of Data Integrity:** The most significant observations noted on the 483 that led to a classification as an OAI by the ORA field investigator, were the failure to report 2 SAEs, including an initial suicide attempt, where the patient was seen in the ER. The failure to report the first suicide attempt was considered a serious finding; however, the finding is mitigated by the fact that the subject did not notify anyone of this attempt, and as such the CI wasn't aware of the event at that time, and could not report it. Other violations noted are unlikely to affect data integrity, and did not compromise subject safety, and are more appropriate for a VAI letter. DSI considers the data as reliable in support of this NDA.

## **2. Steven J. Glass, CRI Worldwide, LLC, 130 White Horse Pike, Clementon, NJ 08021**

**What was inspected:** At this site, 39 subjects were screened, 27 subjects randomized, 12 subjects were discontinued, and 15 subjects completed the study. The inspection reviewed all 39 subject records for signed consent form; and all 27 randomized subjects for IVRS randomization confirmation sheet; the presence of the HAMD-17, MADRS, Quality of Sleep, Clinical/Patient Global Impressions for Visit #2 through Visit #8; discontinuation visit (as appropriate); and out-of-window visits. The inspection reviewed inclusionary criteria for all 14 subjects randomized to study drug; laboratory reports; ECGs; and concomitant medications. The inspection compared the sponsor's data listings to source records for all subjects concerning: early termination, HAMD-17, and serious adverse events.

**General observations/commentary:** Data listing discrepancies observed were minimal, and included mostly adverse event relationships. No serious deficiencies were noted, and no FDA-483 was issued.

**Assessment of data integrity:** In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

**3. John Carman, Carman Research, 4015 S.Cobb Drive, Suite 245, Smyrna, GA 30080**

**What Was Inspected?** All 14 subject records were audited during the study. Of the 14 subjects enrolled, 5 did not complete the study. The inspection compared data listings with the data in the subject records. The data listings consisted of information relating to adverse events, early terminations, and HAMD-17 measurements (Hamilton Rating Scale for Depression). There were no limitations to the inspection.

**Observations/Comments:** The majority of data compared was the same in both data listings and subject files. There were several discrepancies noted, between source documents, and the sponsor's data listings: a) for Subject 106001, the HAMD-17 measurement scored for V5 is listed as '18' in the data listing, whereas in the subject's file, is noted as '9'; b) for Subject 106002, for Visit 2, there was no HAMD-17 scored in the data listing, whereas the subject's file documented a score of '22'; c) for Subject 106006, the Visit 8 HAMD-17 score is listed as '24' in the data listing, whereas it is documented as '22' in the subject's file; d) Review of the file for Subject 106008 revealed that Visit 5 was the last visit for this subject, whereas the data listing identifies a score of '4' for each of Visits 6-8. e) Review of the file for Subject 106012 revealed that Visit 3 was the last visit for this subject. The data listing identifies a score of '20' for each of Visits 4-8. A minor observation was that some telephone visits were conducted either a day early or a day late. No discrepancies were noted during review of the study's drug accountability records.

**Assessment of Data Integrity:** It appears that the CI reported the discrepant items correctly on the CRF; however, the sponsor's data listing was discrepant. No other significant observations were noted during the review of records. In general, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. However, the review division should consider querying the sponsor with respect to the discrepancies in the data listings as identified above.

**4. Dennis J.Munjack, Southwestern Research, Inc., 435 North Bedford Drive, Suite 216, Beverly Hills**

**What was Inspected?** Dr. Dennis Munjack (US Site # 120, Southwestern Research, Inc., California) passed away in the Spring of 2008, and the clinical studies were transferred to Dr. John Murphy, the co-owner of the site. The inspection found that Dr. Munjack had been very active in the conduct of this study and conducted a majority of the clinical evaluations and study questionnaires. The inspection covered eligibility criteria for all 20 subjects enrolled into the study; matched sponsor's data

listings with the records at the site with respect to primary and secondary efficacy endpoints; reviewed adverse events and drug accountability records.

**Observations:** All subjects were found to meet eligibility criteria, with the exception of the one subject cited on the FDA-483. The investigation found that some study visits were out of window, but were adequately documented and communicated to the sponsor; and that some phone visits were out-of-window also, but subject diaries were reviewed for these subjects, and no adverse events were missed. The inspection noted several out-of-window phone visits occurred because the regularly scheduled time fell over a weekend, while the office was closed.

Source documents were organized, legible and complete with signatures and initials and dates. The inspection found drug accountability records documented subjects' exposure to the test article. There were several discussion items: 1) Subject 120-004 had shortness of breath and heartburn recorded in his/her diary. These events were not reported as adverse events; 2) for Subject 120-007, source records documented the subject last used cocaine on 6/7/2007. This subject was randomized into the study on 7/30/2007, and documented as 'not having a substance abuse issue.'

During the discussions, Dr. Murphy was concerned about an item listed on a FDA-483, about the fact that one subject on Prozac, did not have the complete 89 day wash-out period, as required by the protocol. In his response letter, Dr. Murphy stated that in the many years he has conducted anti-depressant clinical trials (~ 200), Prozac has a standard wash-out period of '5 weeks', and he contacted the sponsor to clarify that the intended language in the protocol applied only to the drug Prozac, and not to active metabolite. In this case, Subject 120-021 was randomized into the study approximately 7 weeks after stopping chronic administration of Prozac. This subject was documented as meeting all inclusionary criteria during screening.

**Assessment of Data Integrity:** The inspection found that only one subject did not meet the protocol specified Prozac wash-out period of 89 days. The subject had a wash-out period of only 49 days, so the review division may consider eliminating data from this subject in the overall efficacy analysis. However, for the other subjects, DSI considers the data as valid and acceptable in support of the NDA.

#### **IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

For the 4 clinical investigator sites, the inspections did not reveal any significant findings. DSI recommends the data generated from each site as acceptable in support of this NDA.

*{See appended electronic signature page}*

Sharon K. Gershon, GCP Reviewer  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, Branch Chief  
Good Clinical Practice Branch I/II  
Division of Scientific Investigations

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Sharon Gershon  
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CSO

Tejashri Purohit-Sheth  
5/27/2009 12:30:37 PM  
MEDICAL OFFICER



**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: May 1, 2009

To: Thomas Laughren, MD, Director  
Division of Psychiatry Products

Thru: Kellie Taylor, PharmD, MPH, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Jinhee J. Lee, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Oleptro (Trazodone HCl) Extended-release Tablets  
150 mg and 300 mg

Application Type/Number: NDA 22-411 (IND 76,137)

Applicant/Applicant: Labopharm

OSE RCM #: 2008-1551

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## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review was written in response to a September 24, 2008 request from the Division of Psychiatry Products to review the Applicant's draft container/blister labels, carton and insert labeling. The proposed proprietary name was found acceptable on under the same review number (OSE 2008-1551).

### **1.2 PRODUCT INFORMATION**

Oleptro is the proposed name for Trazodone HCl Extended-release caplets. Trazodone HCl is a serotonin 2A antagonist reuptake inhibitor and is indicated for the treatment of major depressive disorder.

The recommended starting dosage is 150 mg per day. The usual dose is 300 mg per day and the maximum daily dose should not exceed 375 mg. Oleptro should be taken orally at the same time every day in the late evening.

Oleptro will be available as 150 mg and 300 mg tablets.

## **2 METHODS AND MATERIALS**

This section describes the methods and materials used by DMEPA conducting a label, labeling, and/or packaging risk assessment. The primary focus of the 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.<sup>1</sup>

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, 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 Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because the DMEPA staff analyzes reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMEPA uses Failure Mode and Effects Analysis (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> National Coordinating Council for Medication Error Reporting and Prevention.  
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

DMEPA reviewed the following draft labels and labeling submitted by the Applicant on September 18, 2008. See Appendices A through C for pictures of the labels and labeling.

- Container Labels
- Blister Label
- Carton Labeling
- Package Insert Labeling (no image)
- Patient Package Insert/Medication Guide (no image)

### **3 RESULTS**

In the review of the draft container/blister labels, carton and insert labeling of Oleptro, DMEPA focused on safety issues relating to medication errors. DMEPA has identified the following areas of improvement.

Please note that it is difficult to determine the general presentation of information based on the draft labels and labeling provided. Thus, the comments made are general in nature and we may have additional comments once the to-be-marketed labels and labeling are submitted.

#### **3.1 GENERAL COMMENTS**

The draft labels and labeling indicate that the proposed proprietary name is [REDACTED] (b) (4)

The strength appears away from the established name on the blister and container labels.

The labels and labeling for both the 150 mg and 300 mg strengths look identical and it is difficult to differentiate them from one another.

The dosage form appears as “Extended-release Caplet”, however, “caplet” is not a recognized dosage form in the CDER Data Standards Manual.

#### **3.2 CONTAINER LABELS**

See General Comments.

[REDACTED] (b) (4)

#### **3.3 BLISTER LABELS**

See General Comments.

The dosage form statement “Extended-release tablet” has been omitted from the blister labels and does not appear in conjunction with the established name, Trazodone HCl.

#### **3.4 BLISTER CARTON LABELING**

See General Comments.

A “per tablet” statement is not present on the carton labeling.

#### **3.5 PATIENT PACKAGE INSERT/MEDICATION GUIDE**

No comments.

## **4 DISCUSSION**

### **4.1 INCORRECT PROPRIETARY NAME ON LABELS AND LABELING**

The proprietary name is presented as (b) (4) on all of the draft labels and labeling, while the submission indicates that the proposed name is “Oleptro”. Revise the labels and labeling to accurately reflect the correct proposed proprietary name.

### **4.2 EXPRESSION OF ESTABLISHED NAME AND DOSAGE FORM ON CONTAINER/BLISTER LABELS AND BLISTER CARTON LABELING**

The dosage form appears as “Extended-release Caplet. In the How Supplied/Storage and Handling section of the insert labeling, “caplet” is defined as being a “capsule-shaped extended-release tablet”. Since “caplet” is not a recognized dosage form in the CDER Data Standards Manual and because the “caplet” is actually a “tablet”, DMEPA defers to Chemistry, Manufacturing, and Control (CMC) to evaluate the appropriateness of the “caplet” dosage form.

### **4.3 DIFFERENTIATION OF STRENGTH**

The labels and labeling for both the 150 mg and 300 strengths look identical and it is difficult to differentiate them from one another. This lack of differentiation may be due to the fact that the submitted labels/labeling are in draft form. In order to decrease the potential for selection error, the strengths should be differentiated by using color, boxing, or some other means.

### **4.4 CHILD RESISTANT CLOSURE**

It is unclear whether the (b) (4) tablet bottles have a Child Resistant Closure (CRC). Since (b) (4), respectively, they can be considered a unit-of-use bottle based on the dosing of this product. Therefore, ensure that the cap is CRC to be in accordance with the Poison Prevention Packaging Act (PPPA) of 1970.

### **4.5 BLISTER LABELS**

The dosage form statement, “Extended-release XXXX”, has been omitted from the blister labels. Once the appropriate dosage form is identified, this statement should appear in conjunction with the established name as “Trazodone HCl Extended-release XXXX”.

### **4.6 LACK OF “PER TABLET” OR “EACH TABLET CONTAINS” STATEMENT**

A “per tablet” or “each tablet contains” statement is not present on the draft carton labeling. Our post-marketing surveillance has demonstrated that omitting this statement is a source of confusion as patients are misled to believe that the entire contents of the blister equate to the stated strength dose. We are particularly concerned that patients will take all of the 4, 7, or 10 tablets in their respective packaging, thinking it equals the milligram amount of Oleptro expressed on the blister.

## 4.7 PACKAGE INSERT LABELING

(b) (4)

If studies have not been done on the efficacy of the drug product beyond eight weeks, we believe there may potentially be a safety concern. Healthcare providers would not be equipped to field questions from patients regarding the length of treatment. However, we defer evaluation of this statement to the medical officer in the Review Division.

## 5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, DMEPA notes problems with the prominence, presentation, and consistency of information that is vital to the safe use of the product. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.1 and 5.2 that aim at reducing the risk of medication errors.

Additionally, DMEPA defers comments regarding the patient package insert/medication guide to the Division of Risk Management. Please refer to their forthcoming review (OSE Review #2008-1374).

### 5.1 COMMENTS TO THE DIVISION

DMEPA recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), Deborah Desmer (The Project Manager Assigned to the LNC) and the assigned ONDQA Chemist regarding the use of the descriptor “caplet” as the dosage form.

Additionally, we note that in the Dosage and Administration section of the insert labeling, one of the bullets indicates (b) (4)

If studies have not been done on the efficacy of the drug product beyond eight weeks, we believe there may potentially be a safety concern. Healthcare providers would not be equipped to field questions from patients regarding the length of treatment. A statement like this does not seem appropriate and we defer evaluation of this statement to the medical officer in the Review Division.

We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Abolade Adeolu, OSE project manager, at 301-796-4264.

### 5.2 COMMENTS TO THE APPLICANT

We have identified the following areas of needed improvement.

#### A. All Labels and Labeling

1. Revise all labels and labeling so that they accurately reflect the correct proposed proprietary name, Oleptro. Delete the terminology (b) (4)

2. The 150 mg and 300 mg strengths are similar in appearance. It is important to differentiate these labels and labeling to minimize the potential for selection error and confirmation bias. Ensure that the labels and labeling for the 150 mg and 300 mg strengths are differentiated from one another.

**B. Container Labels**

Ensure that the unit-of-use bottles have a Child Resistant Closure (CRC) per the Poison Prevention Packaging Act (PPA) of 1970 to avoid accidental ingestion of Olepro.

**C. Blister Labels**

The dosage form has been omitted from the blister labels. Insert the dosage form statement “Extended-release Caplet”, so that it appears in conjunction with the established name.

**D. Blister Carton Labeling**

Include a statement on the blister carton labeling that provides the per tablet strength (e.g., XXX mg per tablet or each tablet contains XXX mg or add ‘per tablet’ to the current presentation of the strength. Our post-marketing surveillance demonstrates that omitting this statement is a source of confusion as patients are misled to believe that the entire contents of the blister equate to the stated strength dose.

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Denise Toyer  
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Carol Holquist  
5/1/2009 12:27:49 PM  
DRUG SAFETY OFFICE REVIEWER

# DSI CONSULT: Request for Clinical Inspections

**Date:** *See Appended Electronic Signature Page*

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2, HFD-47  
Sharon Gershon, Ph.D., Primary Reviewer  
Division of Scientific Investigations, HFD-45

**Through:** Thomas Laughren, M.D./Division of Psychiatry Products/HFD-130  
Gwenn Zornberg, M.D./ Medical Team Leader

**From:** William Bender, Senior Program Management Officer Consultant  
Division of Psychiatry Products/HFD-130

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA 22-411, N-000

Sponsor/Sponsor contact information: Dhushy Thambipillai

Phone: 1-866-722-6374

[dthambipillai@canreginc.com](mailto:dthambipillai@canreginc.com)

Drug: Trazodone Hydrochloride Extended-Release Caplets

NME: No

Standard or Priority: Standard

Study Population < 18 years of age: no

Pediatric exclusivity: no

Inspection Summary Goal Date: May 1, 2009

Action Goal Date: July 1, 2009

PDUFA: July 18, 2009

## **II. Background Information**

*This new NDA is for the extended-release formulation of Trazodone Hydrochloride (505b2) to treat Major Depressive Disorder.*

## **III. Protocol/Site Identification**

*See Table below for the Protocol Title/# of subjects enrolled and site address:*

Site # (Name and Address)	Protocol #	Number of Subjects	Indication	Reason(s) for Inspection Request
001 Guiseppe Mazza, MD Clinique Medicale Langelier, 6058 Jean-Talon Est, St-Leonard, QC, H1S 3A9	04ACL3-001	40	Major Depressive Disorder	Recruited the highest number of subjects into the study. Exclusion of the data from this site from the study has an appreciable impact on the p-value of primary efficacy analysis.
111 Steven J. Glass, MD CRI Worldwide, LLC 130 White Horse Pike, Clementon, NJ 08021	04ACL3-001	26	Major Depressive Disorder	Recruited a relatively high number of subjects into the study. One of his co-investigators, Dr Howard Hassman, was reported to have deficiencies during previous inspections per CIIL database.
106 John Carman, MD Carman Research 4015 S.Cobb Drive, Suite 245 Smyrna, GA 30080	04ACL3-001	14	Major Depressive Disorder	The PI was reported to have significant deficiencies during previous inspections per CIIL database.
120** Dennis J.Munjack, MD Southwestern Research, Inc. 435 North Bedford Drive, Suite 216, Beverly Hills, CA 90210	04ACL3-001	20	Major Depressive Disorder	Recruited a relatively high number of subjects into the study. The PI was reported to have a deficiency during a previous inspection per CIIL database.

\*\* To be inspected only if resources are available

*Please find the study protocol and a list of the clinical investigator attached at the end of this consult.*

#### **IV. Site Selection/Rationale**

We chose the centers that had the highest number of patients enrolled. Exclusion of the data from site 001 from the study has an appreciable impact on the p-value of primary efficacy analysis. Additionally, there were deficiencies reported during previous inspections regarding sites 111, 106, and 120.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify). Enrollment of large numbers of study subjects. Exclusion of the data from this site from the study has an appreciable impact on the p-value of primary efficacy analysis.

Should you require any additional information, please contact *CDR Bill Bender* at Ph: 301-796-2145 or *Victor Crentsil, MD* at Ph: 301-796-1141.

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Thomas Laughren  
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