CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-411

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022411 **NDA APPROVAL**

Labopharm Canada
Attention: Dhushy Thambipillai
450 North Lakeshore Drive
Mundelein, IL 60060

Dear Ms. Thambipillai:

Please refer to your new drug application (NDA) dated and received on September 18, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oleptro (trazodone hydrochloride) 150 mg and 300 mg Extended Release Tablets.

We acknowledge receipt of your submissions dated July 22, 2009, July 29, 2009, August 10, 2009, September 2, 2009, September 9, 2009, November 11, 2009, January 19, 2010, and January 21, 2010.

The August 10, 2009 submission constituted a complete response to our July 17, 2009 action letter.

This new drug application provides for the use of Oleptro (trazodone hydrochloride) extended-release tablets for the treatment of Major Depressive Disorder.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm155657.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 022411**."

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022411**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Oleptro, for this product.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 6 years because necessary studies are impossible or highly impracticable. This is because Major Depressive Disorder has a very low incidence and prevalence in children less than 6 years of age such that appropriate studies with sufficient number of patients can not be carried out. In addition, it is unlikely that an extended-release formulation of trazodone will satisfy a public health need in the 0- to 6-year-old population.

We are deferring submission of your pediatric studies for ages 7 to 17 years (children and adolescents) for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1564-1 Deferred pediatric study under PREA for the treatment of Major Depressive Disorder in pediatric patients ages 7 to 17 years. A study of safety and efficacy of Oleptro (trazodone hydrochloride) extended release tablets in the relevant pediatric population. Both children (ages 7 to 11 years) and adolescents (ages 12 to 17 years) will be equally represented in the samples, and there will be a reasonable distribution of both sexes in these age strata.

Final Protocol Submission Date:	October 10, 2010
Trial Completion Date:	February 10, 2014
Final Report Submission Date:	February 10, 2015

Submit all clinical protocols to your IND for this product. Submit final study reports to this NDA, 22-411. Use the following designator to prominently label all submissions, including PMR set number **1564-1**: "**Required Pediatric Assessment."**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Oleptro (trazodone hydrochloride) extended release tablets to ensure the benefits of the drug outweigh the risks of suicidality in children, adolescents, and young adults; serotonin syndrome; and QT prolongation.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Oleptro (trazodone hydrochloride) Extended Release Tablets pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Oleptro (trazodone hydrochloride) Extended Release Tablets. FDA has determined that Oleptro (trazodone hydrochloride) Extended Release Tablets is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Oleptro (trazodone hydrochloride) Extended Release Tablets and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Oleptro (trazodone hydrochloride) Extended Release Tablets.

Your proposed REMS submitted on January 15, 2010 and appended to this letter, is approved. The REMS consists of a Medication Guide included with this letter and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. An evaluation of patients' understanding of the serious risks of Oleptro (trazodone hydrochloride) Extended Release Tablets.
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

Assessments of an approved REMS include, under section 505-1(g)(3)(B) and (C), requirements for information on the status of any post approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022411 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022411
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT FOR (NEW INDICATION FOR USE) FOR NDA 022411
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of dose dumping if Oleptro (trazodone hydrochloride) extended release tablets are consumed with alcohol.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1564-2 Dose Dumping and Ethanol Dissolution Study**:** Conduct a study to investigate dose-dumping in the presence of alcohol. To fulfill this request, you should perform *in vitro* dissolution studies for all Oleptro (trazodone hydrochloride) extended-release tablets strengths using the accepted dissolution conditions with the addition of the following alcohol concentrations for the *in vitro* dissolution studies (using 12 units each): 0%, 5%, 10%, 20% and 40%.

The timetable you submitted in an email on October 29, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission Date:	May 11, 2010
Study Completion Date:	November 11, 2010
Final Report Submission Date:	February 11, 2011

Submit the protocol to your IND 71,637 with a cross-reference letter to this NDA. Submit all final reports to your NDA 22-411. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submission**,** as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We

remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

We remind you of the following postmarketing study commitment agreed upon in your communication dated December 16, 2009. The commitment is listed below.

1564-3 Long-Term Efficacy Trial: Conduct and submit the results of a randomized withdrawal clinical trial to address longer-term efficacy for your drug at appropriate doses.

Final Protocol Submission Date:	May 1, 2011
Clinical Trial Completion Date:	November 1, 2013
Final Report Submission Date:	November 1, 2014

We remind you of the following postmarketing study commitment agreed upon in your communication dated January 6, 2010. The commitment is listed below.

1564-4 Dissolution Method and Specifications: The use of 50-75 rpm in USP Type II apparatus with the following dissolution specifications on an interim basis for one year. During this one year period, you are required to revise your dissolution method addressing our above mentioned comments and submit to us for review.

Strength	Dissolution Limits at each timepoint (%)			
	1 hr	6 hrs	12 hrs	20 hrs
150 mg	(b) (4)			
300 mg				

Submit the protocol to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for studies or clinical trials, the number of patients entered into each study or clinical trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence**."

INTERIM DISSOLUTION METHOD & SPECIFICATIONS

Method:

Apparatus:	USP Apparatus II
Paddle Speed:	150 rpm
Medium:	1) Acid stage: 900 mL HCl/NaCl pH 1.2 solution, followed by 2) Buffer stage: 900 mL 50mM phosphate buffer pH 6.0
Temperature:	37±0.5˚C

Specification (150 mg tablet):

Time	Criteria
1 hour	(b) (4)
6 hours	
12 hours	
20 hours	NLT (b) (4)

Specification (300 mg tablet):

Time	Criteria
1 hour	(b) (4)
6 hours	
12 hours	
20 hours	NLT (b) (4)

EXPIRY DATE

An expiration date of 24 months has been granted for the 150 mg and 300 mg tablets.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call CDR Bill Bender, Regulatory Project Manager, at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Package Insert
Medication Guide
Appendix A: REMS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22411	ORIG-1	LABOPHARM INC	TRAZODONE CONTRAMID OAD E-R CAPLET

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

/s/

WILLIAM H BENDER
01/27/2010

THOMAS P LAUGHREN
02/02/2010