CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-745

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
c/o CanReg Inc.
450 North Lakeshore Dr.
Mundelein, IL 60060

Attention: Becky Prokipcak, Ph.D., RAC
Sr. Director, Regulatory Affairs, CanReg Inc.
U.S. Agent for Labopharm Canada, Inc.

Dear Dr. Prokipcak:

Please refer to your New Drug Application (NDA) dated November 25, 2005, received November 28, 2005, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride) Extended-release Tablets 100 mg, 200 mg, and 300 mg.

We acknowledge receipt of your submissions dated December 18, 2006, and January 18, February 8 and 28, March 1, and April 30, 2007.

The December 18, 2006 submission constituted a complete response to our September 28, 2006 action letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiency:

> You have failed to demonstrate the efficacy of Ryzolt for your proposed indication of the management of moderate to moderately severe pain. Your conclusion of efficacy is dependent on the use of imputation strategies for missing data that do not adequately address the problem of good scores being assigned to subjects who dropped out because they were unable to tolerate the product. Provide substantial evidence of efficacy from at least one adequate and well-controlled clinical trial.

We are withholding labeling comments pending resolution of the above deficiency.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

    b. Present tabulations of the new safety data combined with the original NDA data.

    c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

    d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Paul Z. Balcer, Regulatory Project Manager, at (301) 796-1173.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Bob Rappaport
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-745

Labopharm Canada, Inc.
c/o CanReg, Inc.
450 North Lakeshore Dr.
Mundelein, IL 60060

Attention: Becky Prokipcak, Ph.D., RAC
Sr. Director, Regulatory Affairs
U.S. Agent for Labopharm Canada, Inc.

Dear Dr. Prokipcak:

Please refer to your new drug application (NDA) dated November 25, 2005, received November 28, 2005, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ryzolt (tramadol hydrochloride extended-release) Tablets 100 mg, 200 mg, and 300 mg.

We acknowledge receipt of your submissions dated March 1, 20, and 28, April 6 and 7, May 2, 24, 25, and 31, June 12, 16, 20, 23, and 27, July 25, and August 8, 18, 23, and 29, 2006.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies:

1. You have not provided substantial evidence that Ryzolt is effective for your proposed indication of the management of moderate to moderately severe pain. Your conclusion that efficacy has been demonstrated in studies MDT3-003 and MDT3-005 depends on the use of a last observation carried forward (LOCF) imputation methodology for patients who dropped out of the studies. We consider this method of imputing missing data inappropriate, and efficacy was not confirmed when other methods, such as baseline observation carried forward (BOCF) or continuous responder analysis (of the patient's status at the end of the study) were employed. Provide substantial evidence of efficacy from at least one adequate and well-controlled clinical trial. Ryzolt produced at your commercial manufacturing site should be used in future clinical trials.

2. The pharmacokinetic profile of Ryzolt demonstrated low plasma levels of tramadol, compared to Ultram, for a significant portion of time during the proposed 24-hour dosing interval. This finding may be, at best, partially responsible for your inability to demonstrate efficacy in the clinical trials. Provide a discussion, and data as appropriate, to address this concern.

We are withholding package insert comments pending resolution of the above deficiencies.

However, we request that you provide the following revisions to your carton and container at the time of your complete response.

1. The established name proposed includes the term "controlled release." This is not a recognized dosage form in the Unites States Pharmacopeia (USP). The established name for this product is "tramadol hydrochloride extended-release tablets." Revise accordingly.

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

3. Relocate the product strength to appear immediately following the established name. However, assure that the product strength is not in close proximity to the net quantity by relocating the net quantity to the upper right hand corner of the label to prevent confusion.

4. The blue colors used for the boxing of the 200-mg and 300-mg strengths are almost identical. Adjust the box colors to assure that the strengths can be readily differentiated.

5. The dark blue print on the blue background of the cartons of the 200-mg and 300-mg strengths is difficult to read. Revise this color scheme to provide greater contrast between the strength and the background to allow for greater readability and differentiation.

6. For all three strengths, delete the bolding of the number of tablets (i.e. 30 Tablets) to assure that the strength has the most prominence.

7. Decrease the prominence and remove the bolding of the "Rx only" statement to assure that the strength has prominence.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level. **Include an integrated safety dataset from all Phase 3 clinical trials. The variable names in the datasets should be kept consistent across trials.**

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

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d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly 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

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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If you have any questions, call Paul Z. Balcer, Regulatory Project Manager, at (301) 796 1173.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Bob Rappaport
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