DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-315/S-006

Roxane Laboratories
P.O. Box 16532
Columbus, Ohio 43216-653

Attention: Robert Pfeifer, M.S., R.Rh.
Manager, Regulatory Affairs

Dear Mr. Pfeifer:

Please refer to your supplemental new drug application dated April 25, 2000, received April 26, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orlaam (levomethadyl acetate HCl).

This "Changes Being Effected" supplemental new drug application provides for updates in the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the package insert.

We acknowledge your submissions dated October 13, 2000, and February 22, March 13, and 14, 2001.

Reference is also made to the teleconferences on January 3, February 21, March 9, and 19, 2001, to discuss proposed changes to the package insert label, the “Dear Healthcare Professional” letter and the post marketing commitments.

We have completed the review of this supplemental application, as amended, and it is approved effective on the date of this letter. The following changes were agreed upon during the February 21, 2001, teleconference.

1. Place the following information in another box warning at the beginning of the label.

> Due to its potential for serious and possibly life-threatening, proarrhythmic effects, LAAM should be reserved for use in the treatment of opiate-addicted patients who fail to show an acceptable response to other adequate treatments for opiate addiction, either because of insufficient effectiveness or the inability to achieve effective dose due to intolerable adverse effects from those drugs (see Warnings, and Contraindications).
>
> Cases of QT prolongation and serious arrhythmia (torsade de pointes) have been observed during post-marketing treatment with ORLAAM. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of ORLAAM to determine if a prolonged QT interval (QTc greater than 430 [male]

or 450 [female] ms) is present. If there is a prolonged QT interval, ORLAAM should NOT be administered. For patients in whom the potential benefit of ORLAAM treatment is felt to outweigh the risks of potentially serious arrhythmias, an ECG should be performed prior to treatment, 12-14 days after initiating treatment, and periodically thereafter, to rule out any alterations in the QT interval.

ORLAAM should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g. congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia or hypomagnesemia).

ORLAAM is metabolized to active metabolites by the cytochrome P450 isoform, CYP3A4. Therefore, the addition of drugs that induce this enzyme (such as rifampin, phenobarbital, and phenytoin) or inhibit this enzyme (such as ketoconazole, erythromycin, and saquinavir) could increase the levels of parent drug or its active metabolites an a patient that was previously at steady-state, and this could potentially precipitate serious arrhythmias, including torsade de pointes (see PRECAUTIONS, Drug Interactions).

2. Revise the PHARMACOKINETICS section "Metabolism and Elimination" subsection to read as follows.

The cytochrome P450 isoform, CYP3A4, plays a major role in the metabolism of LAAM. As noted above, the formation of nor-LAAM and dinor-LAAM is by sequential demethylation, such that dinor-LAAM is formed from nor-LAAM, not directly from LAAM. While N-demethylation is the primary route of metabolism, minor pathways of elimination include direct excretion and deacetylation to methadol, nor-methadol and dinor-methadol.

3. Revise the INDICATIONS section to read as follows.

ORLAAM is indicated for the management of opiate dependence. ORLAAM should be reserved for the use in treatment of opiate-addicted patients who fail to show an acceptable response to other adequate treatments for opiate addiction, either because of insufficient effectiveness or the inability to achieve effective dose due to intolerable adverse effects from those drugs (see Black Box Warning).

4. Bold the first paragraph in the CONTRAINDICATIONS section.

ORLAAM is contraindicated in patients with known or suspected QT prolongation (QTc interval greater than 430 [male] or 450 [female] ms). This would include patients with congenital long QT syndrome, or conditions

which may lead to QT prolongation (see WARNINGS, Effects on Cardiac Conduction) such as: 1) clinically significant bradycardia (less than 50 bpm), 2) any clinical significant cardiac disease, 3) treatment with Class I and Class III anti-arrhythmics, 4) treatment with monoamine oxidase inhibitors (MAOI's), 5) concomitant treatment with other drug products known to prolong the QT interval (see PRECAUTIONS, Drug Interactions), and 6) electrolyte imbalance, in particular hypokalemia and hypomagnesemia.

5. Revise the first paragraph of the "Effects on Cardiac Conduction" subsection in the WARNINGS section to read as follows.

   ORLAAM has been shown to prolong the ST segment of the electrocardiogram in beagle dogs dosed five days a week and to inhibit the rapidly-activating delayed rectifier current I_{Kr} in isolated myocytes *in vitro*. Serial EKGs performed in a human pharmacokinetics study showed a prolongation of the QTc interval in some patients which was not associated with dose.

6. Revise the last sentence of the second paragraph, in the "Effects on Cardiac Conduction" subsection in the WARNINGS section to read as follows.

   For patients in whom the potential benefit of ORLAAM treatment is felt to outweigh the risks of potentially serious arrhythmias, an ECG should be performed prior to treatment, 12-14 days after initiating treatment, and periodically thereafter, to rule out any alterations in the QT interval.

7. Delete the new paragraph after the second paragraph, in the "Effects on Cardiac Conduction" subsection in the WARNINGS section which stated:

   QTc prolongation and severe arrthythmias have also been seen in patients taking methadone, although the incidence appears to be less when compared to patients taking ORLAAM.

8. Revise the fourth paragraph of the "Effects on Cardiac Conduction" subsection in the WARNINGS section to read as follows.

   ORLAAM is metabolized to active metabolite by the cytochrome P450 isoform. Therefore the addition of drugs that induce this enzyme (such as rifampin, phenobarbital and phenytoin) or inhibit this enzyme (such as ketaconazole, erthromycin, and saquinavir) could increase the levels of parent drug or its active metabolites in a patient that was previously at steady-state, and this could

   potentially precipitate severe arrhythmias, including torsade de pointes (see PRECAUTIONS, Drug Interactions).

9. Revise the "Warnings to Patients" subsection in the WARNINGS section to read as follows.

> Patients must be warned that the peak activity of ORLAAM is not immediate, and that use or abuse of other psychoactive drugs, including alcohol, may result in **fatal** overdose, especially with the first few doses of ORLAAM, either during initiation of treatment or after a lapse in treatment.
>
> Cases of QT prolongation and serious arrhythmia (torsade de pointes) have been observed during post-marketing treatment with ORLAAM. If a patient taking ORLAAM experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, syncope, or seizures), that patient should seek medical attention immediately.

10. Revise the following information throughout the package insert to distinguish between male and female QTc intervals:

> (QTc greater than 430 [male] or 450 [female] ms)

The final printed labeling (FPL) must be identical to the labeling submitted April 25, 2000, and include the agreed upon changes listed above.

Submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-315/S-006." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post marketing study commitments in your submission dated March 13, 2001. These commitments are listed below.

Study 1: *Conduct a study designed to establish the pharmacokinetic interactions between Orlaam and a representative metabolic inducer and a representative metabolic inhibitor, providing for evaluation of the effects of such an interaction on the QT interval.*

> The objective of this study is to elucidate whether *parent drug* is responsible for the cardiac conduction effects of LAAM (in which case, patients on metabolic *inhibitors* would be at risk) or, alternatively, that *metabolites* are responsible for the cardiac conduction effects of LAAM (in which case, patients on metabolic *inducers* would be at risk). The

study should attempt to determine a plasma level for Orlaam or metabolites at which QT prolongation occurs. Note that this study may be unable to establish a minimum threshold for cardiac conduction effects if dramatic drug interactions (i.e. several-fold elevations in Orlaam/metabolite plasma levels) are seen.

Protocol Submission:	Within 4 months of the date of this letter.
Final Report Submission:	Within 2 years following receipt of FDA comments on the new or revised protocols.

Study 2: *Conduct a study to determine the threshold plasma level of Orlaam and/or metabolites at which cardiac conduction effects occur.*

The previous study, ORL0495, does not appear to answer this question. It may be possible to determine the threshold based on data collected in the study to be conducted in fulfillment of study commitment 1. However, if you or the Agency determines that the data from the study conducted in fulfillment of study commitment 1 do not provide the necessary information, then a further study will need to be conducted to fulfill study commitment 2.

Protocol Submission:	Within 4 months of the time that you determine that an additional study is needed.
Final Report Submission:	Within 2 years following receipt of FDA comments on the new protocol.

Study 3: *Study the kinetics of Orlaam in a small number of patients with impairment in excretion of LAAM. This study should characterize the impact of both hepatic and renal impairment unless one of these can be shown to be irrelevant.*

Protocol Submission:	Within 4 months of the date of this letter.
Final Report Submission:	Within 2 years following receipt of FDA comments on the new protocol.

Submit clinical protocols 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 clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

In the February 21, and March 9, 2001, teleconferences, the "Dear Health Care Professional" letter was modified based on the labeling changes. As agreed, the revised letter should be sent immediately to physicians and others responsible for patient care. It is acknowledged that the revised package insert will not be available at the time the letter will be sent. We request that you submit a copy of the revised letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Sara Shepherd, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research