April 11, 2001

IMPORTANT PRESCRIBING INFORMATION FOR ADDICTION TREATMENT SPECIALISTS

Dear Healthcare Professional:

Cases of QT prolongation and severe arrhythmia (including torsade de pointes) have been reported during post-marketing treatment with ORLAAM® (Levomethadyl Acetate Hydrochloride Oral Solution, 10 mg/mL). Roxane Laboratories, Inc. has made important changes to ORLAAM labeling. To date, there have been seven reports of known or suspected torsade de pointes and three additional cases of symptomatic arrhythmia associated with a prolonged QT interval that have been submitted via ongoing safety surveillance activities, out of an estimated 33,000 patients that have been treated with ORLAAM. Therefore, Roxane Laboratories, Inc. has made important changes to the ORLAAM label.

These changes will be implemented within the next several weeks in conjunction with additional revisions made to reflect final regulations (21 CFR Part 291 and 42 CFR Part 8) approved January 17, 2001 for the use of narcotic drugs in maintenance and detoxification treatment of opioid addiction that go into effect on May 18, 2001. In the meantime, we wanted you to be aware of this important safety information in advance of its implementation. The citations below describe where you can find the changes in the package insert when it becomes available in May.

Highlights of the safety changes include the following:

- 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**).

- ORLAAM is contraindicated in patients with known or suspected QT prolongation (QTc interval greater than 430 [male] or 450 [female] ms). **(see Contraindications)** Prior to induction/initiation of ORLAAM therapy, all patients should undergo a 12-lead ECG 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. **(see Warnings - Effects on Cardiac Conduction)**

- For patients in whom the potential benefit of ORLAAM treatment is felt to outweigh the risks of potentially serious arrhythmia, 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. **(see Black Box)**

- Any drug known to have the potential to prolong the QT interval should not be used together with ORLAAM. Possible pharmacodynamic interactions can occur between ORLAAM and potentially arrhythmogenic agents such as class I or III antiarrhythmics, antihistamines that prolong the QT interval, antimalarials, calcium channel blockers, neuroleptics that prolong the QT interval, and antidepressants. Caution should be exercised when prescribing concomitant drugs known to induce hypokalemia or hypomagnesemia as they may precipitate QT prolongation and interact with ORLAAM. These may include diuretics, laxatives and supraphysiological use of steroid hormones with mineralocorticoid potential. **(see Precautions - Drug Interactions)**

- ORLAAM is metabolized to active metabolites by the cytochrome P450 isoform, CYP3A4. Therefore, the addition of drugs that induce or inhibit this enzyme 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 Warnings – Effects on Cardiac Conduction)**

- If a patient taking ORLAAM experiences symptoms suggestive of an arrhythmia (such as palpitations, dizziness, light-headedness, syncope, or seizures), that patient should seek medical attention immediately. **(see Precautions - Information for Patients)**

For patients currently receiving ORLAAM:

- An individualized benefit to risk assessment should be confirmed, taking into account patient presentation and medical history.

- The occurrence of symptoms suggestive of an arrhythmia (such as palpitations, dizziness, light-headedness, syncope, or seizures) should prompt immediate medical evaluation and comprehensive assessment.

For further questions about ORLAAM and these labeling changes, please call Roxane Laboratories Technical Product Information: **1-800-962-8364**.

You can further our understanding of adverse events by reporting all cases to Roxane Laboratories, Inc., by phone at 1-800-962-8364, or to the FDA by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, by mail (using a postage-paid form), or the internet at www.FDA.gov/medwatch.

Sincerely,

Manfred Haehl, M.D.
Senior Vice President
Medical & Drug Regulatory Affairs
Roxane Laboratories, Inc./Boehringer-Ingelheim Pharmaceuticals, Inc