# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**202245Orig1s000**

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

# Risk Evaluation and Mitigation Strategy (REMS) Memorandum
# REMS Retraction

**U.S. FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**
**OFFICE OF NEW DRUGS II**
**DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

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**NDA/BLA #s:** 202245
**Products:** Codeine Sulfate Oral Solution 30 mg/5mL
**APPLICANT:** Roxane Laboratories
**FROM:** Sharon Hertz, M.D., Deputy Division Director
**DATE:** April 21, 2011

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The NDA for Codeine Sulfate Oral Solution 30 mg/5mL was submitted on September 27, 2010. On, December 6, 2010, the applicant was notified that a REMS for Codeine Sulfate Oral Solution 30 mg/5mL was necessary to ensure the benefits of the drug outweighed the risks of medication errors, which may result in life-threatening overdoses. The REMS was to consist of a Medication Guide and a timetable for submission of assessments of the REMS. On January 6, 2011, Roxane Laboratories submitted a proposed REMS in response to our REMS notification letter.

The February 25, 2011 draft Guidance for Industry *Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* states that the FDA may approve a Medication Guide under 21 CFR 208 without requiring the Medication Guide to be a part of a REMS when the Medication Guide is adequate to address the serious and significant public health concern and meets the standard set forth under that regulation.

After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that a REMS for Codeine Sulfate Oral Solution 30 mg/5mL is not necessary to ensure the benefits of the drug outweigh the risks described above because labeling would be adequate to describe the serious risks. The Medication Guide would be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

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/s/

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KATHLEEN M DAVIES
06/30/2011

SHARON H HERTZ
06/30/2011

**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**
**DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS**

## Risk Evaluation and Mitigation Strategy (REMS) Memorandum

DATE: November 15, 2010

NDA #: NDA 202245
PRODUCT: Codeine Sulfate Oral Solution,
APPLICANT: Roxane Laboratories, Inc.

FROM: Sharon Hertz, MD
Deputy Division Director, DAAP

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of Codeine Sulfate Oral Solution, available as 30mg/5mL, outweighs its serious risks of medication errors, such as administering a 30mL dose instead of the prescribed 30mg dose. Such errors have been reported with a similar product used for the same indication, morphine sulfate oral solution, and have resulted in life-threatening overdoses. A 30mL dose of Codeine Sulfate Oral Solution would result in a 180 mg dose.

In reaching this determination we considered the following:

A. It is difficult to estimate the size of the population likely to use Codeine Sulfate Oral Solution, however we estimate that the population is approximately 1 million patients who suffer from acute or chronic pain.
B. Pain is considered a serious condition and can lead to severe disability. Patients with inadequately treated severe pain are at risk for suicide.
C. The expected benefit of the drug is adequate pain relief.
D. The expected duration of treatment is from days to months depending on the underlying disorder causing the pain.
E. The most serious known adverse events related to opioid oral solution formulations are medication errors. For example, Morphine Sulfate is available in 10 mg/5mL, 20 mg/5mL and 20mg/mL. There are reports of prescriptions for a 20 mg dose being administered as a 20 mL dose. If a similar error was made with Codeine Sulfate oral solution 30mg/5mL, and a 30mg dose is administered as 30mL, the patient would receive six times the intended dose, or 180mg of codeine. Patients and caregivers must have information to alert them to this possible error so that they can dispense the correct dose. There are no data to determine a background incidence for this. Codeine Sulfate has been associated with various other adverse effects including death, respiratory depression, CNS depression, severe hypotension, gastrointestinal tract reactions such as nausea, vomiting and diminutive effects on the propulsive peristaltic waves, hypersensitivity reactions including in patients sensitive to sulfites, and the known potential to elevate intracranial pressure and biliary tract pressure. In addition, some individuals are considered ultra-rapid metabolizers of codeine due to a specific CYP2D6 genotype. These individuals convert codeine to its active metabolite, morphine, more rapidly and completely than other people, and this results in higher than expected serum morphine levels. Even at labeled dosage regimens, these people may experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

F. Codeine Sulfate Oral Solution is not a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Codeine Sulfate Oral Solution. FDA has determined that Codeine Sulfate Oral Solution poses 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 Codeine Sulfate Oral Solution. FDA has determined that Codeine Sulfate Oral Solution is a product for which patient labeling could help prevent serious adverse effects, and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use Codeine Sulfate Oral Solution.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

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Sharon Hertz, MD
Deputy Division Director, DAAP

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/s/

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KATHLEEN M DAVIES
12/02/2010

SHARON H HERTZ
12/03/2010