

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201517Orig1s000

RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

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

NDA/BLA #s: 201517
Products: Morphine Sulfate Oral Solution 100 mg per 5 mL (20 mg per mL)
APPLICANT: Lannett Holdings, Inc.
FROM: Sharon Hertz, M.D., Deputy Director
DATE: April 21, 2011

On March 1, 2010, Lannett submitted a proposed REMS to ensure the benefits of the drug outweighed the risks for Morphine Sulfate Oral Solution 100 mg per 5 mL (20 mg/mL). The proposed REMS was amended on and amended on March 26, 2010, and November 17, 2010. The proposed REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The February 2011 draft Guidance for Industry *Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* states that the FDA may approve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 Morphine Sulfate Oral Solution 100 mg per 5 mL (20 mg/mL) 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/

SHARON H HERTZ
06/23/2011

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation II
Division of Anesthesia and Analgesia Products**

DATE: November 29, 2010
NDA #: NDA 201-517
PRODUCT: Morphine Sulfate Oral Solution, 20 mg/mL
APPLICANT: Lannett Holdings, Inc.
FROM: Sharon Hertz, M.D.
Deputy Division Director

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.

There are multiple strengths of Morphine Sulfate Oral Solution available. FDA is aware of post-marketing reports of prescriptions for a 20-mg dose of Morphine Sulfate Oral Solution being administered as a 20-mL dose. A 20-mL dose would result in a 40-mg, 80-mg or 400-mg dose depending on which concentration was available. Such errors have resulted in life-threatening overdoses. The current application is for a 20-mg/mL strength of Morphine Sulfate Oral Solution and the risk for an overdose with dosing errors is greatest at this high concentration.

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 Morphine Sulfate Oral Solution, 20 mg/mL outweigh its serious risks of medication errors resulting in life-threatening overdose.

In reaching this determination we considered the following:

- A. It is difficult to estimate the size of the population likely to use Morphine Sulfate Oral Solution, but somewhere near 200,000 patients for the higher concentration, approximately 1 million patients for the lower concentration formulations.

- B. High concentration morphine oral solution is used for pain that requires higher doses of morphine, generally because of pain that has not responded to lesser doses, in patients who are unable to swallow solid dosage forms. This is considered serious, as patients with inadequately treated pain are at risk for suicide. This formulation of morphine sulfate is also used in the setting of hospice care in terminal patients with pain, also a serious condition.
- C. The expected benefit of the drug, besides the effective pain relief, is that the higher concentration requires a smaller volume for administration. Some patients in pain and, in particular, terminal patients may require large doses of morphine and may not be able to swallow sufficient volume to achieve those doses with lower concentration formulations.
- 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 event with these formulations of morphine sulfate is medication errors. Morphine sulfate is available in 10 mg/5mL, 20 mg/5mL, 20mg/mL (approved under NDA 22-195). There are reports of prescriptions for a 20 mg dose being administered as a 20 mL dose. A 20 mL dose would result in a 40 mg, 80 mg or 400 mg dose depending on which concentration was available. Such errors have resulted in life threatening overdoses. 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. In addition to the reports of medication errors, Morphine Sulfate Oral Solution 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.
- F. Morphine 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 Morphine Sulfate Oral Solution, 20 mg/mL. FDA has determined that Morphine Sulfate Oral Solution, 20mg/mL 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 Morphine Sulfate Oral Solution, 20 mg/mL. FDA has determined that Morphine Sulfate Oral Solution, 20 mg/mL 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 Morphine Sulfate Oral Solution, 20 mg/mL.

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

Sharon Hertz, M.D.

Deputy Division Director, Division of Anesthesia and Analgesia Products

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/s/

SHARON H HERTZ
12/10/2010