

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22382Orig1s000

**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 Rheumatology Products

NDA #: NDA 22-382
Products: Sprix (ketorolac tromethamine) Nasal Spray
SPONSOR: Roxro Pharma Inc.
FROM: Robert Shibuya, MD, Clinical Team Leader
THROUGH: Sharon Hertz, MD, Deputy Division Director
DATE: September 29, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a 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 (NME).

SPRIX (NDA 22-382) contains ketorolac tromethamine, which is in the class of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). The Agency has become aware that use of NSAIDs may increase the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. Risk may increase with duration of use. Additionally, NSAIDs increase the risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Therefore, as of 2005, all prescription NSAIDs have been required to include a Box Warning and Medication Guide as parts of the product label.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Sprix (ketorolac tromethamine) Nasal Spray to ensure that the benefits of the drug outweigh the risks of serious cardiovascular thrombotic events, serious gastrointestinal events, and nephrotoxicity. In reaching this determination, we considered the following:

- A. The estimated number of patients with post-operative pain in the United States could result in the use of the product in a population of tens of millions. This low estimate is based upon statistics from the CDC for ambulatory surgeries in the United States in 2006. <http://www.cdc.gov/nchs/data/nhsr/nhsr011.pdf>.
- B. Post-operative pain can be severe and requires prompt and effective treatment. Ketorolac is a potent NSAID and may be able to manage post-operative pain as monotherapy or in conjunction with opioid analgesia.
- C. The benefits of SPRIX (ketorolac tromethamine) Nasal Spray include analgesia without the risks of respiratory depression, sedation, and addiction.
- D. The product will be used for the short-term (≤ 5 days) management of post-surgical pain.
- E. The most serious of the known adverse events include death, cardiovascular thrombotic events, myocardial infarction, stroke, gastrointestinal bleeding, perforation and ulceration. Ketorolac is recognized as having a less favorable adverse event profile from the perspective of gastrointestinal bleeding which has resulted in the limitation of duration of use.
- F. Sprix (ketorolac tromethamine) Nasal Spray is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Sprix (ketorolac tromethamine) Nasal Spray. FDA has determined that Sprix (ketorolac tromethamine) Nasal Spray 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 SPRIX (ketorolac tromethamine) Nasal Spray. FDA has determined that SPRIX (ketorolac tromethamine) Nasal Spray is a product for which patient labeling could help prevent serious adverse events and 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, SPRIX (ketorolac tromethamine) Nasal Spray.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY

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/s/

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