CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22382Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	22-382/000
Applicant Name	Roxro Pharma, Inc.
Date of Submission	Original application: December 5, 2008 Class 2 resubmission: November 20, 2009
PDUFA Goal Date	May 20, 2010
Proprietary Name / **Established (USAN) Name**	Sprix/Ketorolac tromethamine nasal spray
Dosage Forms / Strength	Intranasal spray/15% solution/15.75 mg/0.1 mL
Proposed Indication(s)	1. For the short term (up to 5 days) management of moderate to severe pain that requires analgesia at the opioid level
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including the following first cycle reviews:	
Medical Officer Review	Robert Levin, M.D.
Statistical Review	Feng Li, Ph.D., Dionne Price, Ph.D.
Pharmacology Toxicology Review	Newton Woo, Ph.D., Adam Wasserman, Ph.D.
CMC Review/OBP Review	Jack Leginus, Ph.D., Prasad Peri, Ph.D.
Microbiology Review	Robert Mello, Ph.D.
Clinical Pharmacology Review	Sayed Al Habet, R. Ph., Ph.D., Suresh Doddapaneni, Ph.D.
DDMAC Review	Twyla Thompson, Mathilda Fienkeng
DSI Review	Susan Leibenhaut, M.D., Tejashri Purohit-Sheth, M.D.
CDTL Review	Robert Shibuya, M.D.
OSE/DMEPA Review	Deveonne Hamilton-Stokes, R.N., BS.N., Todd Bridges, R.Ph.
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This application represents a response to a Complete Response action due to manufacturing deficiencies.

The product is a reformulation of ketorolac tromethamine for use via a novel route, intranasal administration. Ketorolac has been marketed for nearly 20 years and due to safety concerns that arose during postmarketing experience, use has been limited to no more than five days and there are a number of warnings for gastrointestinal bleeding, perioperative bleeding and contraindications for use in pregnancy due to bleeding risk that distinguish this product from other nonsteroidal anti-inflammatory drugs (NSAIDs).

2. Background

The applicant has submitted a 505(b)(1) application for a ketorolac tromethamine product via a new route of administration, nasal spray. Ketorolac has already been approved as a parenteral solution for intravenous and intramuscular administration and as an oral tablet. The reference drug for this application is Toradol, NDA 19-698, approved on November 30, 1989 and the reason this is a 505(b)(1) is that the applicant has submitted a letter providing right of reference to NDA 19-698.

Ketorolac tromethamine nasal spray was developed under IND 62,829 submitted on April 10, 2002.

3. CMC/Device

The issue precluding approval during the prior review cycle was classification of the drug product manufacturer, Hollister Stier Laboratories, as "withhold" following manufacturing site inspections by the Office of Compliance.

As described in the original review, the main issues with respect to cGMP are:

> The Drug Product manufacturer for NDA 22-382, Hollister Stier Laboratories, was inspected for GMP on 1/6/09 to 1/13/09. As a result, an FDA 483 was issued for: stability failures, initiation of practices prior to change approval by the QC Unit, no formal procedure for maintaining segregated vials for non-conforming material, no formal documentation of retention sample review, increase in a product's hold time between (b) (4) without formal approval from CDER, and Annual

Product Reviews were not reviewed by the Quality Unit in a timely manner. The most recent inspection was conducted on 6/19/08 to 7/2/08 and resulted in an FDA 483 for failure to thoroughly review unexplained discrepancies, and a manufacturing process was not thoroughly evaluated to identify and correct possible sources of variability in critical process parameters. Because these issues have not been resolved by Hollister Stier, on 04-Aug-2009, the Office of Compliance made a recommendation of Withhold for the facility.

Dr. Leginus notes in his memo for this review cycle:

- In late December 2009, the Seattle District Office (DO) received a complete response from Hollister Stier Laboratories which was reviewed and determined to adequately address the GMP issues. The DO recommended Acceptable on 22-Jan-2010.
- Based on the District recommendation of Acceptable, the Office of Compliance recommended Acceptable for the drug product manufacturing facility at Hollister Stier Laboratories on 25-Jan-2010.
- Acceptable recommendations have been provided for all manufacturing and testing facilities submitted to EES for NDA 22-382 and an Overall Compliance recommendation of Acceptable was provided on 25-Jan-2010.

Based on this Dr. Leginus recommends approval of this NDA with supervisory concurrence from Dr. Peri.

As noted in my first cycle memo, the remainder of the CMC information submitted in support of the application was adequate. The necessary information about the drug substance was available by reference to Drug Master File (b) (4) which was found to be acceptable. Two identified impurities are adequately controlled at NMT 0.1%.

The drug product is formulated as a solution of ketorolac tromethamine, 15.75 mg/0.1 mL in a clear glass vial with a metered multi-dose spray pump. The drug product is manufactured as a low bioburden buffered solution, under (b) (4) conditions. The applicant does not plan to label it as sterile and the formulation does not contain any antimicrobial agents. EDTA is included as a (b) (4) There is a (b) (4) of (b) (4) of ketorolac plus an additional (b) (4) of ketorolac for the five required priming sprays. The overfill is necessary to ensure an adequate volume for the sprays. An in-use period of one day is necessary due to a reduction in the amount of product delivered beyond the first day of use.

The drug product was found to be photosensitive (b) (4) which provide adequate protection from light. The label will need to state that the product must be protected from light.

I concur with the conclusions reached by the chemistry reviewer and there are no outstanding CMC issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data was submitted in support of this application. The material reviewed in the first cycle was adequate to support the application.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data was submitted in support of this application. Review of the original data demonstrated that the pharmacokinetic profile following use of Sprix is similar in shape to intramuscular ketorolac, with an AUC of 73% and 60% compared to 15 mg and 30 mg intramuscular doses, respectively. The 15 mg and 30 mg doses of intranasal ketorolac are a little less than dose proportional. The use of intranasal oxymetazoline or fluticasone did not later the pharmacokinetic profile. The pharmacokinetic profile in elderly subjects was similar to younger patients with a 10% and 23% increase in Cmax and AUC, respectively. Taken with the greater risk for typical NSAID-associated adverse events in elderly patients, the applicant has proposed a reduction in dosing to 15 mg every 6 to 8 hours rather than 30 mg every 6 to 8 hours. A study of the distribution of the solution after intranasal administration using radiolabeled drug demonstrated that the product was delivered primarily to the nasal cavity and virtually none was delivered to the lungs.

There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

The product is not labeled as sterile and does not contain any antimicrobial agents. Manufacturing of the drug product is under (b) (4) conditions.

There are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

No new efficacy data was submitted to support this application. Efficacy was demonstrated in two Phase 3 studies in patients who had undergone laparoscopy or orthopedic surgery and was further supported in two Phase 2 studies. Details of these studies can be found in the reviews by Drs. Levin and Li, also summarized in my prior memo.

8. Safety

No new safety data was submitted in support of this application. The adverse event profile was similar to the adverse event profile of ketorolac administered by IM and IV routes.

9. Advisory Committee Meeting

There was no advisory committee meeting for this NDA. Ketorolac is not a novel drug substance nor is the use for acute pain novel.

10. Pediatrics

As a new route of administration, the applicant will need to address the requirements of the Pediatric Research Equity Act. The currently approved label for the referenced drug indicates that ketorolac is not indicated in the pediatric population. It is important to note that the use of ketorolac is not contraindicated; it is not recommended because data related to use in pediatrics is owned by Roche who discontinued marketing these products.

Follow review during the first review cycle, the Pediatric Research Committee has agreed that Sprix must be studied from birth to age 16 years, 11 months. If efficacy data are available in the pediatric population for other formulations, efficacy could be bridged using pharmacokinetic data. An alternate route of administration should be considered for the youngest age strata (0-6 months).

11. Other Relevant Regulatory Issues

Audits of the clinical sites did not find any problems that would preclude use of the data based on inspections by the Division of Scientific Investigation.

There are no other unresolved relevant regulatory issues.

12. Labeling

The proprietary name Sprix was found acceptable by the Division of Medication Errors and Prevention.

The labeling was discussed with the applicant. All relevant warnings and contraindications from the Toradol packaging insert will be included in the labeling for Sprix. (b) (4)

There will be a medication guide for this product, the standard NSAID medication guide. This has been reviewed by OSE and has been found to be acceptable. Initially, it was thought that the medication guide would need to be part of a REMS. However, upon reconsideration, the

Office of New Drugs and the Office of Surveillance and Epidemiology agreed that a REMS for Sprix is not required at this time. It was felt that since the REMS is a class REMS for NSAIDs that has not been modified for this product, and that there is no need for additional risk mitigation strategies for this product, the medication guide does not need to be part of a REMS.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The safety and efficacy data submitted support the use of Sprix for the proposed indication. The package insert adequately defines the risk and limitations of use, primarily established from experience with use of ketorolac via intravenous, intramuscular and oral routes.

The problems with the Drug Product manufacturer, Hollister Stier Laboratories, that previously precluded approval have been adequately corrected.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

Deferred pediatric study under PREA for the short term (up to 5 days) management of moderate to severe pain that requires analgesia at the opioid level in pediatric patients ages 0 to 17 years.

Protocol Submission:	October 2011
Study Start:	December 2012
Final Report Submission:	December 2013

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	Sprix (ketorolac tromethamine) nasal spray

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/s/

SHARON H HERTZ
05/14/2010