

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22382Orig1s000

OTHER REVIEW(S)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Deferred pediatric study under PREA for the treatment of 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.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>10/01/2011</u>
	Study/Clinical trial Completion Date:	<u>12/01/2012</u>
	Final Report Submission Date:	<u>12/01/2013</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The studies were deferred because adult studies were completed and ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

No dosing, efficacy, and safety information are available for children for this route of delivery.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, double-blind, controlled safety and efficacy trial. A single- and multiple dose pharmacokinetic trial may be conducted separately or incorporated into the efficacy trial. A minimum of 100 pediatric patients must be exposed in clinical trials.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/

JESSICA M BENJAMIN
05/13/2010

LARISSA LAPTEVA
05/13/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: April 14, 2010

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology
Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Sprix (Ketorolac Tromethamine) Nasal Spray
15.75 mg/spray

Application Type/Number: NDA # 022382

Applicant: Roxro Pharma, Inc.

OSE RCM #: 2010-271

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3	RECOMMENDATIONS	3
3.1	Comments to the Applicant.....	3

1 INTRODUCTION

This review is written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products for the reassessment of labels and labeling for Sprix (Ketorolac Tromethamine) Nasal Spray for their vulnerability to medication errors.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) in our evaluation of the container label, carton labeling and insert labeling that were submitted by the Applicant on November 19, 2009 (see Appendix A thru C; no image of insert labeling).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be clarified and improved upon to minimize the potential for medication errors. Section 3.1 (*Comments to the Applicant*) contains our recommendations for the container label and carton labeling. We request these recommendations be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Bola Adeolu, OSE Regulatory Project manager, at 301-796-4264.

3.1 COMMENTS TO THE APPLICANT

A. *Container Label*

1. Revise the proprietary name, established name, dosage form and product strength to appear in the following format. Healthcare practitioners are accustomed to this layout and variance from it may result in difficulty in identifying this important information. In order to ensure there is room for this presentation, decrease the size of the proprietary name, as currently presented it utilizes half of the principle display panel.

Sprix
(Ketorolac Tromethamine)
Nasal Spray
15.75 mg per spray

2. As currently presented, the established name still does not appear to be one half the size of the proprietary name. Ensure the prominence of the established name is in accordance with 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
3. Delete the statement [REDACTED] ^{(b) (4)} as this information is not useful and will provide space on the label to include the discard statement below (Comment A4).

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

4. Prominently include the statement on the principle display panel: “Discard 24 hours after first dose, even if drug product remains”. This will help ensure the product is used as intended. If space does not permit, consider presenting the statement horizontally on the right side panel.

B. Carton Labeling (1 count)

1. See Comment A2.
2. In order to increase readability, insert a line space between the dosage form and strength and between the strength and route of administration. As currently presented this information appears crowded.
3. Increase the prominence of the product strength.
4. Relocate the “Dispense the accompanying Medication Guide to each patient” to the principle display panel, so that this information is not overlooked.
5. De-bold and relocate the “Rx only” statement to the bottom of the principle display panel, in order to make room for the Medication Guide Statement.
6. Increase the prominence by bolding the statement: “Discard 24 hours after first dose, even if drug product remains”. This will help ensure the product is used as intended and that the statement is not overlooked.

C. Carton Labeling (5 count)

1. See Comment A2.
2. See Comments B3, B4, and B6.
3. Insert a line space between the dosage form and product strength.
4. “ROXRO” is rather prominent. Decrease the size and prominence of “ROXRO” in order to help ensure there is adequate room for the above recommendations.

3 pages of draft labeling has been withheld as B(4) CCI/TS immediately following this page

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/

DEVEONNE G HAMILTON-STOKES
04/14/2010

TODD D BRIDGES
04/14/2010

DENISE P TOYER
04/15/2010

CAROL A HOLQUIST
04/15/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 5, 2009

To: Bob Rappaport, M.D., Division Director
**Division of Anesthesia, Analgesia, and
Rheumatology Products**

Through: Claudia Karwoski, PharmD, Division Director
Division of Risk Management
Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: LaShawn Griffiths, MSHS-PH, BSN, RN, Acting Team
Leader
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide,
and Instructions for Use) and Proposed Risk Evaluation
and Mitigation Strategy (REMS)

Drug Name(s): Sprix (ketorolac tromethamine) Nasal Spray
Application
Type/Number: NDA 22-382

Applicant/sponsor: Roxro Pharmaceuticals
OSE RCM #: 2009-182

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG), Patient Instructions for Use (IFU), and Risk Evaluation and Mitigation Strategy (REMS) for Sprix (ketorolac tromethamine) Nasal Spray. Please let us know if DAARP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Sprix (ketorolac tromethamine) Prescribing Information (PI) submitted January 13, 2009 and revised by the Review Division throughout the current review cycle.
- Draft Sprix (ketorolac tromethamine) Medication Guide (MG) and Instructions for Use (IFU) submitted on January 13, 2009.
- Proposed Sprix (ketorolac tromethamine) Risk Evaluation and Mitigation Strategy (REMS), dated May 18, 2009

3 RESULTS OF REVIEW

In our review of the MG and IFU, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG and IFU meet the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

In our review of the proposed REMS, we have ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act of 2007.

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with MG, IFU, and the elements of the REMS with revisions provided in this review.

Please note, the timetable for submission of the assessments is required to be approved as part of the REMS, but not the Applicant's proposed

information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments **do not** need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

Comments to DAARP:

Our annotated MG and IFU is appended to this memo (Appendices A and B). Any additional revisions to the PI should be reflected in the MG and IFU.

Comments for Sponsor:

See the appended Sprix REMS proposal (Appendix C of this memo) for track changes corresponding to comments below.

a. GOAL

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of NSAID medicines including Sprix (ketorolac tromethamine) Nasal Spray.

b. The Medication Guide distribution plan is generally acceptable. We have some editorial comments in this section of the proposed REMS.

c. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable. We have some editorial comments in this section of the proposed REMS.

d. Please submit for review a detailed plan to evaluate patients' understanding about the safe use of Sprix (ketorolac trmethamine) Nasal Spray. Your detailed plan should be submitted as part of the REMS supporting document. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS Correspondence." If you plan to conduct this assessment using a survey, your submission should include:

- All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of Sprix (ketorolac trmethamine) Nasal Spray. This should include, but not be limited to:
 - Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)
 - The expected number of patients to be surveyed
 - How the participants will be recruited
 - How and how often the surveys will be administered

- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Please let us know if you have any questions.

22 pages of draft labeling has been withheld as B(4) CCI/TS immediately following this page

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/s/

LASHAWN M GRIFFITHS
10/05/2009

CLAUDIA B KARWOSKI
10/05/2009
concur

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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	Study/Clinical trial Completion Date:	<u>02/05/2010</u>
	Final Report Submission Date:	<u>10/05/2012</u>
	Other:	<u>MM/DD/YYYY</u>

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- Meta-analysis or pooled analysis of previous studies/clinical trials
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Agreed upon:

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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/

JESSICA M BENJAMIN
09/30/2009

LARISSA LAPTEVA
10/01/2009

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-382 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Sprix Established/Proper Name: nasal ketorolac tromethamine Dosage Form: nasal spray Strengths: 15% solution		
Applicant: Roxro Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: 12/5/09 Date of Receipt: 12/5/09 Date clock started after UN:		
PDUFA Goal Date: 10/05/09		Action Goal Date (if different):
Filing Date: 2/17/09 Date of Filing Meeting: 1/8/09		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): short term management of moderate to severe pain		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): (b) (4)	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aip.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
User Fee Status Comments:	<input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> http://www.fda.gov/cder/ob/default.htm If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES # years requested: 3 years</p> <p><input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
Format and Content			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>			
<p>If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
PREA	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Comments:	

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): 12/13/04 <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): 10/4/07 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/08/09

NDA: 22-382

PROPRIETARY/ESTABLISHED NAMES: Sprix/ nasal ketorolac tromethamine

APPLICANT: Roxro Pharmaceuticals

BACKGROUND:

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jessica Benjamin	Y
	CPMS/TL:	Sara Stradley	N
Cross-Discipline Team Leader (CDTL)	Rob Shibuya		Y
Clinical	Reviewer:	Robert Levin	Y
	TL:	Rob Shibuya	Y
Social Scientist Review <i>(for OTC products)</i>	Reviewer:		
	TL:		
Labeling Review <i>(for OTC products)</i>	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology <i>(for antimicrobial products)</i>	Reviewer:		
	TL:		

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Clinical Pharmacology	Reviewer:	Sayed Al Habet	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Joan Beunconsejo	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Newton Woo	Y
	TL:	Adam Wasserman	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Joe Leginus	Y
	TL:	Ali Al Hakim	N
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES: Sharon Hertz, Deputy Director
Bob Rappaport, Director

505(b)(2) filing issues? If yes, list issues:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Bob Rappaport</p> <p>GRMP Timeline Milestones: Midcycle 4/30/09, Wrap up 7/29/09</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <ul style="list-style-type: none"> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

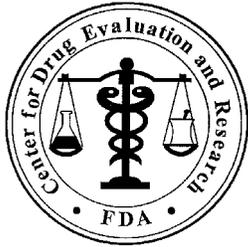
If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA M BENJAMIN

09/10/2009



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: September 8, 2009

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology
Products

Through: Todd Bridges, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Deveonne Hamilton-Stokes, RN, BSN, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Sprix (Ketorolac Tromethamine) Nasal Spray
15.75 mg per spray

Application Type/Number: NDA # 22-382

Applicant: Roxro Pharma, Inc.

OSE RCM #: 2008-2052

CONTENTS

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2	METHODS AND MATERIALS.....	3
3	RECOMMENDATIONS	3
3.1	Comments to the Applicant.....	3

1 INTRODUCTION

This review is written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products for assessment of labels and labeling for Sprix (Ketorolac Tromethamine) Nasal Spray.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) to evaluate the following label and labeling:

Container label submitted July 17, 2009 (Appendix A)

Carton labeling (1 bottle and 5 bottles) submitted August 24, 2009 (Appendix B and C)

Insert labeling submitted January 13, 2009 (No image)

3 RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be clarified and improved upon to minimize the potential for medication errors. Section 3.1 (*Comments to the Applicant*) contains our recommendations for the container label and carton labeling. We request that these recommendations be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Bola Adeolu, OSE Regulatory Project manager, at 301-796-4264.

3.1 COMMENTS TO THE APPLICANT

A. *Container Label*

1. Revise the proprietary name, established name, dosage form and product strength to appear in the following format. Healthcare practitioners are accustomed to this layout and variance from it may result in difficulty in identifying this important information. In order to ensure there is room for this presentation, decrease the size of the proprietary name, as currently presented it utilizes half of the principle display panel.

Sprix
(Ketorolac Tromethamine)
Nasal Spray
15.75 mg per spray

2. Ensure the established name is one half the size of the proprietary name and has a prominence commensurate to the proprietary name, per 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

3. Delete the (b) (4) which follows the dosage form on the principle display panel and that follows the established name on the side panel. This medication will not be ordered in terms of percentage and thus the product strength should be presented as 15.75 mg per spray to minimize confusion.
4. Relocate the net quantity away from the dosage form.
5. Revise to include the route of administration “For Intranasal Use Only” per 21 CFR 201.100(b)(3).
6. Due to the limited size of the container label, delete the usual dosage statement in order that more essential information such as the discard instructions can be presented.
7. Include the statement: “Discard 24 hours after first dose, even if drug product remains”. This will help ensure the product is used as intended.
8. (b) (4) to “Refrigerate at 2°C to 8°C (36°F to 46°F) until dispensed”. This will help ensure that this important information is not overlooked and stability is not compromised by incorrect storage.

B. Carton Labeling (b) (4)

1. Revise the proprietary name, established name, dosage form and product strength to appear in the following format. Healthcare practitioners are accustomed to this layout and variance from it may result in difficulty in identifying this important information. Note that this presentation does not include the (b) (4). Additionally, increase the prominence of the product strength.

Sprix
(Ketorolac Tromethamine)
Nasal spray
15.75 mg per spray

2. Ensure the established name is one half the size of the proprietary name and has a prominence commensurate to the proprietary name, per 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
3. Delete the (b) (4) which precedes the dosage form throughout the carton labeling and that follows the established name on the side panel. This medication will not be ordered in terms of percentage and thus the product strength should be presented as 15.75 mg per spray to minimize confusion.
4. Revise to include the route of administration “For Intranasal Use Only” on the principle display panel per 21 CFR 201.100(b)(3).
5. Ensure the net quantity statement is not located near the product strength.
6. Relocate the manufacturing information to the side panel in order to include the statement: “Discard 24 hours after first dose, even if drug product remains” on the principle display panel. This will help ensure the product is used as intended.
7. Per 21 CF 201.55, revise the (b) (4) to read: “Usual dosage: See package insert for dosage information” since it is not possible to present a complete statement of dosage for this product in the space available.

8. Revise the Fahrenheit temperature range from 26-46° to 36°F to 46°F, which is the temperature range for a refrigerator per the USP. Additionally revise the word (b) (4) to “Refrigerate” as this will help ensure that this important information is not overlooked and stability is not compromised by incorrect storage.
9. Your labels and labeling will require a statement alerting the dispenser to provide a Medication Guide with the product. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
 1. “Dispense the enclosed Medication Guide to each patient.” or
 2. “Dispense the accompanying Medication Guide to each patient.”
10. Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided with each “usual” or average dose. For example:
 1. A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
 2. A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

C. Carton Labeling (b) (4)

1. See Carton Labeling Comments B1 through B4 and B6 through B10.
2. Delete the stand-alone statement (b) (4). This statement may be interpreted as the net weight of the contents of the carton (i.e., 5 bottles of nasal spray).
3. On the blue panel which will be used as the nasal spray holder, include the statement, “Discard 24 hours after first dose, even if drug product remains” as this will serve as an additional reminder for patients.
4. Revise the total net quantity statement from (b) (4) to read: “Contains 5 bottles. Each bottle contains a 1 day Supply”.

2 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEVEONNE G HAMILTON-STOKES
09/08/2009

TODD D BRIDGES
09/09/2009

CAROL A HOLQUIST
09/09/2009



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Maternal Health Team (MHT) Review

Date: September 2, 2009 **Date Consulted:** August 14, 2009

From: Richardae Araojo, Pharm.D.
Regulatory Reviewer, Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Analgesia, Anesthesia, and Rheumatology Products (DAARP)

Drug: NDA 22-382; Sprix (ketorolac tromethamine) Nasal Spray

Subject: Lactation Labeling

Materials Reviewed: Nursing Mother's subsection of proposed Sprix labeling.

Consult Question: Please review the Nursing Mother's subsection of the Sprix label.

INTRODUCTION

On December 5, 2008, Roxro Pharma, Inc submitted a new drug application (NDA 22-382) for Sprix (ketorolac tromethamine) nasal spray to the Division of Analgesia, Anesthesia, and Rheumatology Products (DAARP). The proposed indication for Sprix is for short term (up to five days) inpatient management of moderately severe pain (b) (4). DAARP requested the Maternal Health Team's (MHT) review of the Nursing Mothers subsection of the proposed label.

BACKGROUND

Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits cyclo-oxygenase (COX) resulting in reduced synthesis of prostaglandins, thromboxanes, and prostacyclin. Ketorolac is currently marketed in various dosage forms including an oral tablet, intravenous and intramuscular injection, and ophthalmic solution. Sprix is a new proposed nasal spray formulation of ketorolac for inpatient treatment of moderately severe pain for no more than five days.

The current approved labeling for oral and injection forms of ketorolac products includes a boxed warning and contraindication for use in nursing mothers because of potential adverse effects of prostaglandin inhibiting drugs on neonates. The Maternal Health Team is not aware of the rationale that led to a nursing contraindication.

In December 2007, DAARP consulted the MHT to revise the Pregnancy and Nursing Mothers subsections of NSAID class labeling (see MHT review dated February 22, 2008). This review provides labeling recommendations on the divisions proposed ketorolac label based on NSAID class labeling and available data on ketorolac use during lactation.

REVIEW OF DATA

Published Literature on Lactation

To determine if human data are available on the use of ketorolac during lactation, a PubMed search was performed using the following search terms:

- Ketorolac and lactation
- Ketorolac and breastfeeding
- Ketorolac and neonatal adverse effects
- Ketorolac and infant adverse effects

In addition, the following sources were used to gather information on ketorolac use during lactation:

- National Library of medicine's Drugs and lactation Database (LactMed)
- TERIS – The teratogen Information System
- REPROTOX

A summary of the most relevant data regarding ketorolac use during lactation is presented below.

- 1. Wischnik A, Manth SM, Lloyd J, Bullingham R, Thompson JS. The excretion of ketorolac tromethamine into breast milk after multiple oral dosing. Eur J Clin Pharmacol 1989; 36:521-524.**

Ten women (between 22 and 35 years of age) two to six days postpartum were given oral ketorolac 10 mg, four times daily for two days. Infants were not allowed to breastfeed during the study. Breast milk and maternal blood samples were collected before the first dose, two and six hours after the first dose, four hours after the second dose, and two hours after the third dose. Breast milk was obtained from both breasts using an electric pump.

Ketorolac was undetectable (<5 ng/ml) in the breast milk of four patients. In the remaining six patients, ketorolac was detectable two hours after the first dose on days one and two. The ketorolac concentrations in milk ranged from 5.2 ng/ml to 7.9 ng/ml. On study days one and two, ketorolac milk concentrations, six hours after the first dose, were below the assay limit in all patients. On study day one, four hours after dose two, only two patients had detectable ketorolac concentrations in milk of 4.8 ng/ml. For the six women who had measurable ketorolac milk concentrations, the milk: plasma ratios ranged from 0.015 – 0.037. The authors state that assuming a breast milk intake of 400 or 1000 ml per day, a breastfed infant would receive 3.16 to 7.9 mg/day of ketorolac.

Reviewer comments:

- *This publication contained a misprint regarding the units of the estimated infant daily dose of ketorolac from breast milk.^{1,2} The correct dosage units are mcg/day, i.e. 3.16 to 7.9 mcg/day. This calculation was based on an assumption that a breastfed infant consumes up to 1000 ml of breast milk per day. However, the standardized mean milk consumption for a fully breastfed infant is 150 mL/kg/day. Therefore, the estimated maximum infant daily dose of ketorolac from breast milk in an exclusively breastfed infant is 1.185mcg/kg/day.*
- *Data from this study is included in the Nursing Mothers section of approved ketorolac labeling and in the divisions proposed labeling for Sprix.*

In addition to the data summarized above, the American Academy of Pediatrics (AAP) considers ketorolac to be “usually compatible with breastfeeding”.³

(b) (4)

DISCUSSION AND CONCLUSIONS

Sprix is a new proposed nasal spray formulation of ketorolac for inpatient treatment of moderately severe pain for no more than five days. The current approved labeling for oral and injection forms of ketorolac products includes a boxed warning and contraindication for use in nursing mothers because of potential adverse effects of prostaglandin inhibiting drugs on neonates.

Breastfeeding women commonly use NSAIDs and/or opioids to treat postpartum pain, and pain due to other conditions. Infants exposed to opioids through breastmilk may have increased sedation, respiratory depression, and may develop opiate dependence. These infants may also experience withdrawal symptoms when maternal opioid use is stopped. Maternal NSAID use is not associated with these adverse reactions in nursing infants. The major adverse reactions in adults associated with use of ketorolac or other NSAIDs are decreased renal function or renal failure, gastric mucosal damage that may result in ulceration and/or bleeding, and hematologic abnormalities including inhibition of platelet aggregation.

There is only one published study on the use of ketorolac (40mg/day oral) in breastfeeding women. In this study, ketorolac concentrations in milk ranged from undetectable (<5 ng/ml) to 7.9 ng/ml. Based on these concentrations, the estimated maximum infant daily dose of ketorolac from breast milk is 1.185mcg/kg/day. No adverse reactions were reported in the nursing infants. It is important to note that the oral ketorolac dose in this study was 40 mg/day and the maximum recommended daily dose of Sprix is 126 mg/day. Based on data from this study and an assumption that a breastfeeding infant consumes about 1000 ml of breast milk per day; a breastfeeding infant would receive 0.2% of a maternal ketorolac dose.² In addition, the AAP considers ketorolac to be “usually compatible with breastfeeding”.⁴

⁴ Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108:776-789.

Ketorolac injection is indicated for use in children as young as two years old, and while not a labeled indication, ketorolac and other NSAIDs are used in neonates to treat patent ductus arteriosus and post-operative pain. The maximum approved dose of ketorolac in children two years of age is 30 mg (intramuscular dose) or 15 mg (intravenous dose).

Based on available human lactation data and use of ketorolac in neonates, there are no data to support a box warning or contraindication for ketorolac use in nursing mothers. Breast milk provides significant health benefits to developing infants and is considered the optimal form of infant nutrition. Therefore, the benefits of breastfeeding may outweigh the potential risks of infant exposure to small amounts of ketorolac through breast milk.

In addition, the MHT noted that the division's proposed pregnancy category for Sprix is category C prior to 30 weeks gestation and category D starting at 30 weeks gestation. The two-category recommendation is consistent with draft NSAID class labeling. While the ketorolac preclinical data are negative for adverse developmental outcomes, animal dosing was limited by maternal toxicity. Therefore these animal studies do not adequately assess ketorolac's potential to cause adverse developmental outcomes in humans. On this basis, a pregnancy category C is appropriate for first and second trimester ketorolac use instead of the category B that would normally be chosen based on negative animal studies. This category C designation is consistent with labeling for other NSAIDs when used prior to 30 weeks gestation. Based on human data, NSAIDs are pregnancy category D for use at and after 30 weeks gestation due to an increased risk for premature closure of the ductus arteriosus and resulting fetal morbidity and mortality.

The Division and the sponsor included a contraindication for use in "late pregnancy." Drug use in pregnancy should only be contraindicated for pregnancy category "X" drugs, drugs where the benefits of use never outweigh the risks and human and/or animal data demonstrate an increased potential for adverse developmental outcomes. While use of NSAIDs in the third trimester is associated with an increased risk of premature closure of the ductus arteriosus, maternal benefit may outweigh fetal risk in certain situations. This is the basis for the pregnancy category "D" designation for use at and beyond 30 weeks gestation.

The MHT suggested changes to the Pregnancy and Nursing Mothers subsections of Sprix labeling and other recommendations are provided below.

RECOMMENDATIONS

1. The boxed warning and contraindication for use in the nursing mothers section should be removed from labeling for all ketorolac products.
2. Information about the increased risk associated with use of ketorolac nasal spray at and beyond 30 weeks gestation should be included as a "warning" and not as a "contraindication." This is consistent with a pregnancy category "D" designation rather than a category "X" designation.

3. Sprix should be assigned a pregnancy category C for use before 30 weeks gestation (based on animal dosing limitations in negative developmental toxicology studies) and pregnancy category D for use at and beyond 30 weeks gestation for the increased risk of premature closure of the ductus arteriosus (based on human data). Provided in Appendix A are the MHT's recommended revisions to the Divisions proposed Pregnancy labeling for Sprix. This labeling should be considered for all oral and injection forms of ketorolac.
4. Provided in Appendix A are the MHT's recommended revisions to the Divisions proposed Nursing Mothers labeling for Sprix. This labeling should be considered for all oral and injection forms of ketorolac.
5. Nursing mothers labeling for some NSAID products is inconsistent with available published data. DAARP should consider consulting the MHT to review available lactation data for NSAID products and provide recommendations for labeling.

(b) (4)

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/s/

RICHARDAE T ARAOJO
09/04/2009

Karen B FEIBUS
09/04/2009

I agree with the content and recommendations contained in this review.

LISA L MATHIS
09/09/2009
Concur

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

DATE: August 21, 2009

To: Jessica Benjamin – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer
Twyla Thompson – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

for Mathilda Fienkeng

Through: Michael Sauer – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 22-382 SPRIX™ (ketorolac tromethamine) Nasal Spray

DDMAC has reviewed the proposed product labeling (PI), Medication Guide, for SPRIX™ (ketorolac tromethamine) Nasal Spray, submitted for consult on January 27, 2009.

The following comments are provided using the updated proposed PI and Medication Guide sent via email on August 14, 2009 by Jessica Benjamin. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

28 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

MATHILDA K FIENKENG
08/25/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 29, 2009

TO: Sharon Jessica Benjamin, Regulatory Project Manager
Robert Levin, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-382

APPLICANT: Roxro Pharma

DRUG: Sprix (Ketorolac tromethamin nasal spray)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: management of moderate to severe pain, (b) (4)
(b) (4) for short-term use; up to 5 days

CONSULTATION REQUEST DATE: January 23, 2009

DIVISION ACTION GOAL DATE: October 5, 2009

PDUFA DATE: October 5, 2009

I. BACKGROUND:

Roxro Pharma has submitted NDA 22-382 for Ketorolac Tromethamine nasal spray. This is a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of this application. The sponsor proposes the indication of management of moderate to severe pain, (b) (4) for short-term use, up to 5 days.

Clinical inspections were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. The primary efficacy endpoint for both trials was the summed pain intensity difference (SPID), measured by visual analog scale (VAS) at 6 hours after the first dose of study medication. The SPID is calculated by adding the weighted PID scores over the specified interval where the weight assigned each PID is proportional to the elapsed time in hours since the previous evaluation. The review division requested verification of efficacy out to 48 hours.

For Protocol 2005-01, sites were chosen by high enrollment, geographic location, and inspectional history. Protocol 2003-01 was conducted at a single site.

The protocols inspected include:

- A. Protocol 2003-01 entitled, “A Phase 3, Double-blind, Randomized Study of the Safety, Tolerability, and Analgesic Efficacy of Multiple Doses of Ketorolac Tromethamine Administered Intranasally for Postoperative Pain”; and
- B. Protocol 2005-01 entitled, “A Phase 3, Double-blind, Randomized Study of the Safety, Tolerability, and Analgesic Efficacy of Multiple Doses of Ketorolac Tromethamine Administered Intranasally for Postoperative Pain Following Major Abdominal Surgery”

II. RESULTS (by Site):

Name of Clinical Investigator (CI), and Location	Protocol # and # of Subjects:	Inspection Date	Final Classification
CI #1 Dr. John Moodie Waikato Clinical Research 226 Pembroke Street Hamilton, New Zealand	ROX 2003-01/ 300 subjects	June 15 to 19, 2009	NAI
CI #2 Neil K. Singla, M.D. Department of Anesthesia Lotus Clinical Research, Inc. Huntington Hospital 100 W. California Blvd. Pasadena, CA 91105	ROX 2005-01/ 91 subjects	May 28, to June 2, 2009	NAI
CI#3 Harold S. Minkowitz, M.D. 921 Gessner Road, Suite 226 Houston, TX 77024-2501	ROX 2005-01/ 64 subjects	March 23 to 27, 2009	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

1. Dr. John Moodie
Waikato Clinical Research
226 Pembroke Street
Hamilton, New Zealand
 - a. **What was inspected:** This was the only site for Protocol 2003-01. There were 373 subjects screened, 300 enrolled, and 211 subjects completed the study. An audit of 103 subjects' records was conducted. For verification of the primary endpoint, all visual analog scale (VAS) points (including the single-dose study) from baseline to 48 hours were verified for 47 subjects and all VAS points (not including the single-dose study) from baseline to 48 hours were verified for 103 subjects.
 - b. **General observations/commentary:** Consult to DSI requested the inspection of Dr. Colin Brown at this site. The FDA inspection found that Dr. Moodie was the principal investigator and (b) (4) had been a subinvestigator. All subjects had signed consent forms. No regulatory violations were noted and there was no under-reporting of adverse events. The occurrence of two adverse events, constipation in Subject #81193 and drowsiness in Subject #81190, were

reported by the study site to the sponsor/CRO, but are not included in the line listings submitted to the NDA.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Neil K. Singla, M.D.
Department of Anesthesia, Lotus Clinical Research, Inc.
Huntington Hospital
100 W. California Blvd.
Pasadena, CA 91105

- a. **What was inspected:** For Protocol 2005-01 at this site, 104 subjects were consented, and 91 subjects participated in the study. Twelve subjects were early terminated due to adverse events or nursing error, or lost to follow-up. An audit of all subjects' records was conducted to compare case report forms with hospital source records. A review of 23 subject diaries was conducted to verify the primary endpoint.
- b. **General observations/commentary:** There was no under-reporting of adverse events and the primary endpoint was verified. No regulatory violations were noted.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Harold S. Minkowitz, M.D.
921 Gessner Road, Suite 226
Houston, TX 77024-2501

- a. **What was inspected:** For Protocol 2005-01 at this site, 76 subjects were consented, twelve subjects withdrew or were discontinued, and 64 subjects completed the study. An audit of 17 of the 64 subjects' records was conducted to verify protocol compliance, adverse event reporting and the primary endpoint. Records for all of the seven screen failures were reviewed.
- b. **General observations/commentary:** There was no under-reporting of adverse events and the primary endpoint was verified. No regulatory violations were noted.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections of all clinical sites did not find regulatory violations. The study appears to have been conducted adequately, and the data generated by all sites may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
07/30/2009

TEJASHRI S PUROHIT-SHETH
07/30/2009

DSI CONSULT: Request for Clinical Inspections

Date: January 22, 2009

To: Leslie Ball, M.D., Branch Chief, GCP2
Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Bob Rappaport, Division Director
Division of Anesthesia, Analgesia, and Rheumatology Products,
HFD-170

From: Sharon Jessica Benjamin, Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products,
HFD-170

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-382
Sponsor/Sponsor contact information (to include phone/email): Roxro Pharma/Bonnie Horner,
phone: 650-947-9776, e-mail: bonniehorner@abcglobal.net
Drug: Ketorolac tromethamine nasal spray
NME: No
Standard or Priority: Standard
Study Population < 18 years of age: No
Pediatric exclusivity: N/A

PDUFA: October 5, 2009
Action Goal Date: October 5, 2009
Inspection Summary Goal Date: August 4, 2009

II. Background Information

Include a brief introduction about the application and include the following:

- *New application or supplement? Reason for supplement*
- *Proposed indication*

DSI Updated 12/2007

- *Brief information*
 - *on drug*
 - *disease*
 - *pivotal studies (to include brief summary of protocols, pertinent endpoints, and concerns with application)*

The Applicant has submitted an NDA for an intranasal (IN) spray containing 15.75 mg ketorolac tromethamine per spray (2 sprays (one spray per nostril) delivers 31.5 mg) for the relief of moderate to severe pain. The pivotal studies include two Phase 3 pain studies (Protocol ROX 2005-01 and Protocol ROX 2003-01) conducted in patients with postoperative pain.

Protocol ROX 2005-01 was a randomized, double-blind, placebo-controlled, Phase 3 study of IN ketorolac in subjects who underwent major abdominal surgery. Following surgery, subjects exhibiting signs of discomfort received IV opioid titrated to comfort. Once subjects were alert and able to complete pain assessments, they were randomized 2:1 to receive IN ketorolac 30 mg or IN placebo when their pain intensity rating was greater than or equal to 40 mm on a 100-mm visual analog scale (VAS). Thereafter, subjects were to have received study drug every 6 hours for 48 hours and then up to 4 times daily for up to 5 days total. The primary efficacy endpoint was the SPID 6. However, we are interested in efficacy out to 48 hours; please verify the efficacy data to that point.

Protocol ROX 2003-01 was a randomized, double-blind, placebo-controlled, Phase 3 study similar in design to study ROX 2005-01. However, patients in this study had abdominal, orthopedic and other surgeries. Subjects were dosed with study drug every 8 hours. The primary efficacy measure in this study was also the SPID 6. However, we are interested in efficacy out to 48 hours; please verify the efficacy data to that point.

III. Protocol/Site Identification

Include the Protocol Title/# for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol #/Title	Number of Subjects	Indication
<p>Site #81 Colin Brown, BSc, MB, BS, FANZCA (Principal Investigator) Telephone: 647-839-8634 Fax: 647-839-8744 Email: waiclres@xtra.co.nz</p> <p>Waikato Clinical Research 226 Pembroke Street Hamilton, New Zealand (07) 839 8899 ext 7604</p> <p>(Entire study conducted at this site)</p>	<p>ROX 2003-01 A Phase 3, double-blind, randomized study of the safety, tolerability, and analgesic efficacy of multiple doses of ketorolac tromethamine administered intranasally for postoperative pain</p>	<p>300</p>	<p>Short-term management of moderate to severe pain</p>
<p>Site #81 Colin Brown Same contact information as above</p> <p>Waikato Clinical Research 226 Pembroke Street Hamilton, New Zealand</p>	<p>ROX 2005-01 A Phase 3, Double-Blind, Randomized Study of the Safety, Tolerability, and Analgesic Efficacy of Multiple Doses of Ketorolac Tromethamine Administered Intranasally for Postoperative Pain Following Major Abdominal Surgery</p>	<p>82 (Total enrollment 321 in USA and NZ)</p>	<p>Short-term management of moderate to severe pain</p>
<p>Site #82 Neil Singla, MD Telephone: 626-397-3507 Fax: 626-397-2165</p> <p>Clinical Management Services Huntington Memorial Hospital 100 West California Blvd. Pasadena, CA 91105</p>	<p>ROX 2005-01 Same Title</p>	<p>91</p>	<p>Same</p>

Site # (Name,Address, Phone number, email, fax#)	Protocol #/Title	Number of Subjects	Indication
Site #83 Harold Minkowitz, MD Telephone: 713-242-3436 Fax: 713-242-3664 Memorial City Hospital 921 Gessner Anesthesia Department Houston, TX 77024	ROX 2005-01 Same Title	64	Same

IV. Site Selection/Rationale

Site #81 in New Zealand was selected since all the patients studied in pivotal Study ROX 2003-01 and a substantial number of the subjects in Study ROX 2005-01 were enrolled at this site. Study sites # 82 and #83 were selected since the highest US enrollment was at these two sites.

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data (one pivotal study was conducted entirely outside the USA)
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

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/s/

Robert A. Levin
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