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RESEARCH**

APPLICATION NUMBER:
22382Orig1s000

OTHER ACTION LETTER(s)



NDA 022382

COMPLETE RESPONSE

Roxro Pharma, Inc.
535 Middlefield Road
Suite 180
Menlo Park, CA 94025

Attention: Roger Whiting, PhD
President and Chief Scientific Officer

Dear Dr. Whiting:

Please refer to your new drug application (NDA) dated December 5, 2008, received December 5, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Sprix™ (ketorolac tromethamine) Nasal Spray.

We acknowledge receipt of your amendments dated December 12, 2008, and January 8, 13, and 28, February 5, 16, and 27, April 29, May 4(2) and 20, June 12, 23, and 29, July 1, 3, and 17, August 4, 13, 20, and 24, and September 3, 28, and 30, 2009.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

1. During a recent inspection of Hollister-Stier Laboratories facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

LABELING

2. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a

clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

3. Submit draft carton and container labeling revised as follows:

Container Label

- a. 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

- b. 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.
- c. 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 (b) (4) and thus the product strength should be presented as 15.75 mg per spray to minimize confusion.
- d. Relocate the net quantity away from the dosage form.
- e. Revise to include the route of administration “For Intranasal Use Only” per 21 CFR 201.100(b)(3).
- f. 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.
- g. Include the statement: “Discard 24 hours after first dose, even if drug product remains”. This will help ensure the product is used as intended.

- h. Revise (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.

Carton Labeling (b) (4)

- i. 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

- j. 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.
- k. 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.
- l. Revise to include the route of administration “For Intranasal Use Only” on the principle display panel per 21 CFR 201.100(b)(3).
- m. Ensure the net quantity statement is not located near the product strength.
- n. 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.
- o. 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.

- p. 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.
- q. 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.”
- r. 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.

Carton Labeling (b) (4)

- s. See Carton Labeling comments i through l and n through r.
- t. 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).
- u. 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.
- v. Revise the total net quantity statement from (b) (4) to read: “Contains 5 bottles. Each bottle contains a 1 day Supply”.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and

clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert

26 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	KETOROLAC TROMETHAMINE NASAL SPRAY

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

/s/

SHARON H HERTZ
10/05/2009