DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 200652

Roxane Laboratories, Inc.
Attention: Gregory M. Hicks
Associate Director
1809 Wilson Road
Columbus, Ohio 43228

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received on October 14, 2009, and submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Alosetron Hydrochloride Tablets, 0.5 mg and 1.0 mg.

Reference is also made to the Complete Response letter issued by this office on July 19, 2013, and to your amendments dated September 17 and December 18, 2013; January 15, February 26, March 18, April 1, April 10, April 25, May 9, May 27, June 5, June 24, July 8, 2014; and February 18, February 25, March 16, March 20, March 27, April 1, and April 17, 2015.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Alosetron Hydrochloride Tablets, 0.5 mg and 1.0 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Lotronex Tablets of Prometheus Laboratories, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, Lotronex Tablets, 0.5 mg and 1.0 mg, of Prometheus Laboratories, Inc. (Prometheus), is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 6,284,770 (the '770 patent), is scheduled to expire on October 5, 2018.

Your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '770 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Alosetron Hydrochloride Tablets, 0.5 mg and 1.0 mg, under this ANDA.[1] You have notified the agency that Roxane Laboratories, Inc. (Roxane) complied with the requirements of

[1] We note that the '770 patent was not listed in the Orange Book when your ANDA was received, and your paragraph IV certification was submitted in an amendment to your ANDA received on December 2, 2010. Therefore litigation with respect to this patent is not a bar to approval of your ANDA.

section 505(j)(2)(B) of the Act, and that litigation was initiated against Roxane for infringement of the '770 patent in the United States District Court for the District of New Jersey [Prometheus Laboratories Inc. v. Roxane Laboratories Inc., Civil Action Nos. 2:11-cv-00230 and 2:11-cv-01241]. You have also notified the agency that the court decided that '770 patent is invalid.

With respect to 180-day generic drug exclusivity, we note that Roxane was the first ANDA applicant for Alosetron Hydrochloride Tablets, 0.5 mg and 1.0 mg, to submit a substantially complete ANDA with a paragraph IV certification to the '770 patent. Therefore, with this approval, Roxane may be eligible for 180 days of generic drug exclusivity for Alosetron Hydrochloride Tablets, 0.5 mg and 1.0 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The agency notes that Roxane failed to obtain tentative approval of this ANDA. See section 505(j)(5)(D)(i)(IV) (forfeiture of exclusivity for failure to obtain tentative approval). The agency is not, however, making a formal determination at this time of Roxane's eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after Roxane begins commercial marketing of Alosetron Hydrochloride Tablets, 0.5 mg and 1.0 mg, or (b) at any time prior to the expiration of the '770 patent if Roxane has not begun commercial marketing. Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

The details of the REMS requirements were outlined in our REMS notification letter dated July 28, 2011. In that letter, you were also notified that pursuant to section 505-1(i) of the FDCA, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use unless FDA waives that requirement.

You submitted a request for the FDA to grant a waiver from the requirement to have a single shared system REMS with the reference listed drug under section 505-1(i)(1)(B) of the FDCA, dated March 15, 2013, and amended September 17, 2013; February 25, 2015; March 16, 2015; March 20, 2015; March 27, 2015; April 1, 2015; and April 17, 2015.

Your request for a waiver has been granted with the following two conditions:

1. Your waiver-granted REMS system shall be open to all current and future sponsors of ANDAs or NDAs for alosetron hydrochloride products.

2. FDA is limiting the grant of the waiver to a term of three years. If, at the end of the three-year period, Roxane seeks to continue marketing pursuant to the waiver, the Agency will evaluate whether an extension of the waiver is appropriate at that time.

Your proposed REMS, submitted on July 12, 2011, and final amendment dated April 17, 2015, appended to this letter, is approved.

The REMS consists of a Medication Guide, elements to assure safe use (ETASU), and an implementation system.

Your REMS must be fully operational before you introduce Alosetron Hydrochloride Tablets into interstate commerce.

Under sections 505-1(g)(2)(C), FDA can require the submission of a REMS assessment if FDA determines that an assessment is needed to evaluate whether the approved strategy should be modified to ensure the benefits of the drug outweigh the risks of the drug or to minimize the burden on the health care delivery system of complying with the REMS. Additionally, the details for what should be included in your REMS assessments and the dates of the REMS assessments are listed in Appendix 1.

We remind you that section 505-1(f)(8) of the FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify the submission containing a proposed modification of the REMS or any REMS assessments with the following wording in bold capital letters at the top of the first page of the submission:

ANDA 200652
REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 200652
PROPOSED REMS MODIFICATION

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

Carol A. Holquist -S

Digitally signed by Carol A. Holquist -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300052464, cn=Carol A. Holquist -S
Date: 2015.05.04 10:21:57 -04'00'

Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Appendix 1
REMS
Medication Guide

Appendix 1

Dates for submission of waiver-granted REMS assessments

Roxane will submit REMS Assessments to FDA six (6) and 12 months following REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Roxane will submit each assessment so that it will be received by the FDA on or before the due date.

REMS Assessment Plan

The REMS Assessment Plan includes, but is not limited to, the following:

a. The number of certified prescribers in the Alosetron REMS Program that have undergone certification during the reporting period and cumulatively.
b. The number of prescribers who are removed from enrollment in the Alosetron REMS Program during the reporting period due to noncompliance.
c. The number of prescribers not enrolled in the Alosetron REMS Program who are writing prescriptions for alosetron and whether pharmacists are filling prescriptions written by prescribers not enrolled in the Alosetron REMS Program.
d. Corrective and preventative actions taken to address non-compliance with distribution and dispensing requirements during the reporting period and cumulatively.
e. Alosetron drug use patterns during the reporting period and cumulatively, to include reasons for use, patient demographics, and prescribing medical specialists.
f. The number of cases of ischemic colitis, ischemic colitis involving ischemic changes, ischemia, or necrosis of the colon; constipation requiring hospitalization or emergency room visit; possible complications of constipation such as obstruction, perforation, intestinal ulceration, toxic megacolon, ileus or impaction resulting in hospitalization or emergency room visit; and all reports of death, regardless of causality, during the reporting period and cumulatively.
g. The narrative summary, tabular analyses and discussion of the above cases (in “f.”) received during the reporting period including the clinical significance of these events.
h. An evaluation of prescribers, pharmacists, and patients’ understanding of the serious risks of alosetron. Results of surveys of physicians’, patients’, and pharmacists’ understanding of the serious risks of alosetron are due with the second REMS assessment, at 12 months, and all subsequent REMS assessments.
i. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
j. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.