DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-107/S-005

GlaxoSmithKline
Attention: Olivia Pinkett, Ph.D.
Product Director, Regulatory Affairs
P.O. Box 13398
Five Moore Drive
Research Triangle Park, North Carolina 27709-3398

Dear Dr. Pinkett:

Please refer to your supplemental new drug application dated December 7, 2001, received December 7, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex (alosetron hydrochloride) Tablets, 1 mg. We acknowledge receipt of your submissions dated January 16, 30, and 31; February 1 and 27; March 1 and 22; April 9 and 30, 2002; May 15 and 20, 2002; and June 3, 5, and 6, 2002.

Lotronex was originally approved February 9, 2000, and, subsequently, you voluntarily withdrew the drug from the market after you received reports of ischemic colitis and severe complications of constipation associated with use of the drug. This supplemental application, considered for approval under 21 CFR 314, Subpart H at your request, narrows the original approved indication to use of the drug in a population for whom the benefits of the drug may outweigh the risks and provides for a risk management program.

This supplemental application provides for the use of Lotronex only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

- chronic IBS symptoms (generally lasting 6 months or longer),
- had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and
- failed to respond to conventional therapy.

Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:

- frequent and severe abdominal pain/discomfort
- frequent bowel urgency or fecal incontinence
- disability or restriction of daily activities due to IBS

We have completed our review of this supplemental application, as amended, and have concluded that adequate information has been presented to approve a supplemental application for Lotronex (alosetron hydrochloride) Tablets, 1 mg, under 21 CFR 314 Subpart H. You have indicated your agreement with approval under restricted conditions. Accordingly, this supplemental application is approved under 21 CFR 314, Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of all FDA regulations and the specific restrictions on distribution and use described below.

Lotronex Risk Management Program

We remind you that your Lotronex Risk Management Program is an important part of the postmarketing risk management for Lotronex, and must include each of the following components:

1. Enrollment of qualified physicians in a physician prescribing program.

2. Implementation of a program to educate physicians, pharmacists and patients about the risks and benefits of Lotronex.

3. Implementation of a reporting and collection system for serious adverse events associated with the use of Lotronex that complies with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

4. Implementation of a plan to evaluate the effectiveness of the Lotronex risk management program.

The Lotronex Risk Management Program, as described in the attached documents, adequately addresses each of these requirements. Any changes to the program must be discussed with FDA prior to its institution and is subject to FDA approval. We expect your continued cooperation to resolve any problems regarding the Lotronex Risk Management Program that may be identified following approval of this supplement.

Within the first year of the initiation of the risk management program, and annually thereafter, you must provide FDA with a report under 21 CFR 314.81(b)(2) that describes how each element of the program has been implemented, provides implementation data, and evaluates the success of the program using, among other available data, the studies described in the attached Risk Management Program and post marketing commitments #7 and #8 below.

We remind you of your specific reporting obligations regarding serious adverse events in patients who have received Lotronex. As set forth in the attached document, in addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80 (c)), you will initiate a 15-day report for each of the following:

- All spontaneous reports of ischemic colitis
- All spontaneous reports involving ischemic changes, ischemia, or necrosis of the colon
- All spontaneous reports involving constipation requiring hospitalization or emergency room visit
- All spontaneous reports involving possible complications of constipation such as obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, or impaction resulting in hospitalization or emergency room visit
- All spontaneous reports of death, regardless of causality

Post Marketing Commitments

You have committed to conduct postmarketing studies, specified in your submissions dated June 3 and 6, 2002, that are listed below. The commitments listed below replace all previous postmarketing study commitments associated with the original NDA.

1. Conduct a randomized, double-blind, placebo-controlled study in women with severe diarrhea-predominant IBS to determine efficacy and safety of lower doses of Lotronex. The doses to be studied are: 0.5mg QD, 1mg QD, 1mg BID and placebo.

   Protocol Submission: August 2002
   Study Start: First Quarter 2003
   Final Report Submission: Fourth Quarter 2005

2. Conduct a randomized, blinded, dose-titration study in women with severe diarrhea-predominant IBS to determine efficacy and safety "as needed" (prn) dosing of Lotronex. The study arms are: 0.5mg tablets (0-4 tablets) prn vs. placebo prn; and, 1mg BID continuous dosing vs. placebo BID continuous dosing.

   Protocol Submission: August 2002
   Study Start: First Quarter 2003
   Final Report Submission: Fourth Quarter 2005

3. Obtain blood samples prospectively in patients enrolled in at least the studies described under commitments #1 and #2 above, to allow DNA analysis to 1) identify SNPs or haplotypes that predict adverse events in patients who develop ischemic colitis and 2) determine genotype of polymorphic CYP enzymes (CYP 1A2 and 2C9) responsible for Lotronex metabolism.

Protocol Submission: August 2002
Study Start: First Quarter 2003
Final Report Submission: Second Quarter 2006

4. Propose and conduct mechanistic studies to investigate the pathophysiologic etiology of Lotronex-induced ischemic colitis and small bowel ischemia.

   Protocol Submission: September 2002
   Study Start: Fourth Quarter 2002
   Final Report Submission: First Quarter 2004

5. Conduct protocol #S3B10946 entitled, "An open-label, parallel-group, pharmacokinetic and tolerability study of a single 1mg dose of alosetron in hepatically-impaired subjects and in healthy control subjects," as amended on October 25, 2001.

   Protocol Submission: September 2002
   Study Start: Second Quarter 2003
   Final Report Submission: Second Quarter 2005

6. Conduct a pharmacokinetic drug-drug interaction study to evaluate the effect of administration of fluvoxamine, 100mg BID and ketoconazole 200mg BID (7 days of dosing) on the pharmacokinetics of a single dose of 1mg Lotronex in at least 12 healthy females.

   Protocol Submission: September 2002
   Study Start: First Quarter 2003
   Final Report Submission: Third Quarter 2003

7. Conduct a study to periodically (at least quarterly) compare prescribing of physicians enrolled in the prescribing program for Lotronex with all Lotronex prescribing identified in a general prescription data base (e.g., IMS). GlaxoSmithKline and FDA will review the study findings and agree to educational and/or other activities that may be needed to address observations.

   Protocol Submission: September 2002
   Study Start: First Quarter 2003
   Final Report Submission: June 2009

8. Conduct the study as submitted on May 15, 2001, amended June 3, 2002, entitled, "An Epidemiologic Program for the Study of the Safety and Utilization of Lotronex in Medical Practice in the U.S." to 1) evaluate compliance with use of the Patient-Physician Agreement form as a means to ensure patients have severe diarrhea-predominant IBS and been counseled on the risks and benefits of Lotronex, 2) examine appropriate use of Lotronex 3) survey patient knowledge and understanding about the risks of Lotronex, 4) monitor serious gastrointestinal adverse events and deaths associated with Lotronex use, as well as estimate risks associated with long-term use of Lotronex, and 5) evaluate risk factors for serious gastrointestinal adverse events. GlaxoSmithKline and FDA will review study findings and agree to educational and/or other activities that may be needed to address observations.

   Protocol Submission: September 2002
   Study Start: First Quarter 2003
   Final Report Submission: June 2009

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final study reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

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Pursuant to 21 CFR Part 208, based on postmarketing information and information provided in this supplemental application, FDA has determined that Lotronex poses a serious and significant public health concern requiring distribution of a Medication Guide. This Medication Guide is necessary for patients' safe and effective use of Lotronex. FDA has determined that Lotronex is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Lotronex. In addition, patient labeling could help prevent serious adverse events related to constipation.

The final printed labeling (FPL) must be identical to the enclosed agreed upon labeling text submitted on June 5, 2002, for the Product Information insert, Medication Guide, Patient-Physician Agreement form, and Physician Attestation form; and identical to the immediate container and carton labels submitted on May 20, 2002. Marketing the product with FPL with text that is not identical to the agreed upon approved text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-107**." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. Submit all proposed materials in draft or mock up form, not final print. Send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the labeling directly to:

Division of Drug Marketing, Advertising
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on postmarketing experience and the information submitted in this supplemental application, we do not believe it is appropriate to conduct studies in pediatric patients at this time. Therefore, under 21 CFR 314.55, we are deferring submission of studies for pediatric patients of all ages because such studies should be delayed until additional safety and effectiveness data have been collected and reviewed. If, at a later date, we determine that pediatric studies are necessary or appropriate, we will notify you.

If you have any questions, call Paul Levine, Jr., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure