LOTRONEX RISK MANAGEMENT PROGRAM

A. Prescribing Program

1. GlaxoSmithKline will enroll in a prescribing program physicians who meet all of the following qualifications:

   i. Ability to diagnose and treat IBS.
   ii. Ability to diagnose and manage ischemic colitis.
   iii. Ability to diagnose and manage constipation and the complications of constipation.
   iv. Understand the risks and benefits of Lotronex treatment for severe diarrhea-predominant IBS, including the information in the package insert, Medication Guide, and Patient-Physician Agreement.

   Physicians may self-attest to meeting these prescribing qualifications. GlaxoSmithKline's receipt of the physician attestation form will precede distribution of Lotronex prescribing materials to the physician.

2. GlaxoSmithKline will enroll in the prescribing program physicians who agree to do each of the following:

   i. Educate patients about the risks and benefits of Lotronex therapy and give each patient a copy of the Medication Guide.

      The Patient-Physician Agreement form will be used to demonstrate that physicians fulfill this responsibility. Physicians who prescribe Lotronex will be asked to agree to obtain the patient's signature on the form, co-sign the form, place the original signed form in the patient's medical record, and give a copy to the patient.

   ii. Report serious adverse events to GlaxoSmithKline or to the Food and Drug Administration's MedWatch Program.

   iii. Participate in a system that will identify for pharmacists the physicians who are enrolled in the GlaxoSmithKline Lotronex prescribing program

3. GlaxoSmithKline will provide a way for patients and pharmacists to identify physicians that are enrolled in the Lotronex prescribing program.

   i. GlaxoSmithKline has proposed to supply stickers to enrolled physicians who will affix them to all their Lotronex prescriptions (i.e., original and all subsequent refill prescriptions) so that pharmacists can identify that prescriptions were written by physicians enrolled in the program.

   ii. GlaxoSmithKline will have a process to facilitate patient access to enrolled physicians.

B. Educational Program

GlaxoSmithKline will implement a program to educate physicians, pharmacists, and patients about the risks and benefits of Lotronex. This program will contain each of the following:

1. Educational opportunities will be provided to physicians to obtain prescribing qualifications and to carry out physician responsibilities under the Lotronex prescribing program as stated in the Physician Attestation form.

2. Pharmacists will be educated about the risks and benefits of Lotronex, information in the approved labeling (including the package insert and the Medication Guide), the program for verifying prescriptions were written by physicians enrolled in the Prescribing Program for Lotronex, recommendations that they not accept telephone, facsimile, or computerized prescriptions for Lotronex, and dispensing of the Medication Guide.

3. Patients will be educated on the risks associated with the use of Lotronex, the signs and symptoms of ischemic colitis and constipation that could lead to serious consequences, and Lotronex's approved indication.

4. The following materials will be submitted to FDA for review and comment by October 30, 2002: educational materials for physicians; educational plan and materials for pharmacists; educational plan and materials for patients.

C. Adverse Event Reporting:

GlaxoSmithKline will implement 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). Under 21 CFR 314.80(c), the following will be submitted to FDA as 15-day reports, and a summary and discussion of the clinical significance of these events will be provided in the periodic report:

- 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

D. Risk Management Evaluation

GlaxoSmithKline will implement a program to evaluate the effectiveness of the overall risk management program in assuring that Lotronex is used safely. This information will allow the Agency to assess, on an ongoing basis, whether Lotronex continues to be safe for use under the conditions of use upon which Lotronex is being approved. The program will include each of the following elements:

1. A study to evaluate whether physicians not enrolled in the Lotronex prescribing program are writing prescriptions and whether pharmacists are filling prescriptions written by physicians not enrolled in the program.

2. A study to evaluate the effect of the Lotronex Risk Management Program on use of Lotronex by patients with severe diarrhea-predominant irritable bowel syndrome, patient knowledge of risks of Lotronex, and frequency of serious gastrointestinal adverse events and death associated with Lotronex.

3. An annual report, submitted in accordance with 21 CFR 314.81(b)(2), beginning with the submission (within the first year of initiation of the risk management program) of the annual report under that regulation, 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 paragraphs D1 and 2 above.