IMPORTANT DRUG WARNING

RE: Safety-related Revisions to Labeling for LOTRONEX® (alosetron hydrochloride) Tablets
Important New Dispensing Information; Issuance of a Patient Medication Guide

Dear Health Care Professional:

Glaxo Wellcome Inc. is writing to inform you of important new safety information reflected in recent changes to the labeling for Lotronex (alosetron hydrochloride), a serotonin 5-HT3 antagonist indicated for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS). This new safety information pertains to reports of constipation, that in a few cases have resulted in serious sequelae, and infrequent reports of ischemic colitis occurring in association with the use of Lotronex. To help ensure that patients are informed of this important and significant safety information, the "Information for Patients" that was previously provided as a tear-off section of the prescribing information has been changed to a Medication Guide. This Medication Guide has been approved by the Food and Drug Administration and a copy of the Medication Guide is required to be given to patients when LOTRONEX is dispensed.

At the time of approval of Lotronex in February 2000, the labeling included warnings of occurrences of ischemic colitis and, dose-related occurrences of constipation that had been reported in clinical trials. Subsequently, we have received post-marketing reports of a few cases of serious complications of constipation, including obstruction, perforation, impaction, toxic megacolon, and secondary ischemia, in patients treated with Lotronex. In some cases these complications have required intestinal surgery, including colectomy. Since approval, a few additional cases of ischemic colitis have also been reported. These cases of ischemic colitis are comparable in frequency and severity to those reported prior to approval.

To communicate this important information to health care professionals, the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION** sections of the package insert for Lotronex have been revised to highlight information about constipation and ischemic colitis. Important safety-related changes include the following:

- **CONTRAINDICATIONS**:

Lotronex should not be initiated in patients experiencing constipation.
Lotronex is contraindicated in patients:

- With a history of chronic or severe constipation or with a history of sequelae from constipation.
- With a history of intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions.
- With a history of ischemic colitis.
- With current or a history of Crohn's Disease or ulcerative colitis.
- With active diverticulitis
- With a known hypersensitivity to any component of the product.

- The **WARNINGS** section has been revised to include information about infrequent reports of serious complications of constipation, including obstruction, perforation, impaction, toxic megacolon, and secondary ischemia, in association with alosetron administration. In some cases these complications have required intestinal surgery, including colectomy.
  Lotronex should be discontinued immediately and not restarted in patients who experience severe constipation while receiving the drug. Patients with non-severe constipation should be closely monitored. Cases of non-severe constipation can be managed with an interruption of therapy or usual care including laxatives. However, if constipation does not resolve within four days with these measures, treatment should be discontinued and not resumed.

- The **WARNINGS** section of the labeling also describes the incidence of ischemic colitis in female subjects in clinical trials as approximately 1 in 700 patients. Lotronex should be discontinued immediately in patients with signs of ischemic colitis. These patients should be evaluated promptly and have appropriate diagnostic testing performed. Treatment with Lotronex should not be resumed in patients who have developed ischemic colitis**.**
- The Information for Patients subsection of the **PRECAUTIONS** section of the labeling has been revised to provide direction to the healthcare provider concerning discussions with the patient about Lotronex.
- The **DOSAGE AND ADMINISTRATION** section has been revised to include recommendations regarding situations where treatment with Lotronex should be interrupted or discontinued because of constipation.

Copies of the revised prescribing information and the patient medication guide are enclosed.

Glaxo Wellcome is committed to providing you with the most current product information for Lotronex. You can assist us in monitoring the safety of Lotronex by reporting adverse reactions to Glaxo Wellcome at 1-888-825-5249 to the FDA MedWatch program by telephone at 1-800-332-1088, by FAX at 1-800-332-0178, via www.FDA.gov/medwatch, or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Please refer to the enclosed complete prescribing information for Lotronex. Additional copies of the Patient Medication Guide are enclosed for you to distribute to patients. If you have any questions about the new information or want additional information about Lotronex, or if you want additional copies of the enclosed information for patients, please contact the Glaxo Wellcome Customer Response Center at 1-888-825-5249.

Sincerely,

Richard S. Kent, MD
Vice President and Chief Medical Officer