QUESTIONS AND DISCUSSION ITEMS FOR LOTRONEX® TABLETS

FDA Gastrointestinal Drugs Advisory Committee
27 June 2000

Lotronex® (alosetron hydrochloride) Tablets were approved for marketing by the Food and Drug Administration (FDA) on February 9, 2000 for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea. Since the approval of Lotronex®, FDA has received additional reports of gastrointestinal serious adverse events associated with use of the drug. These serious adverse events include reports of major complications of constipation, of ischemic colitis, and of hepatic toxicity.

Prescription drugs have both benefits and risks. FDA and the pharmaceutical industry have a responsibility to the public to reduce exposures to risks and their adverse consequences (risk management). The assessment of a drug's benefits and risks is specific to the drug's effectiveness, the disease or condition being treated, and the nature, frequency, and severity of adverse events associated with the drug's use. While information is not complete, new adverse event data for Lotronex® suggest a need to reevaluate its benefit-risk profile and the need to intervene to promote safety.

At this meeting, FDA seeks the Committee's advice in four general areas: (1) defining appropriate goals and outcomes of a risk-management program for Lotronex®, (2) identifying interventions that should be implemented as part of a risk-management program for Lotronex®, (3) clarifying how the impact of such interventions can be best evaluated, and (4) specifying next steps if the risk-management program for Lotronex® does not meet its desired goals. In addition, FDA is seeking the Committee's comments in these four areas on the risk-management plan proposed by Glaxo Wellcome for management of constipation, ischemic colitis, and hepatic toxicity associated with the use of Lotronex®.

1. **Goals and outcomes of a risk-management plan for Lotronex®**

   a. Please discuss the specific safety goals and outcomes you would like to see achieved through implementation of a risk-management program for Lotronex®. For example, does the Committee believe the most appropriate risk-management goal should be:

      I. dissemination of this new safety information about Lotronex®? If so, how broadly and to whom?

      ii. assuring that patients at high risk for toxicities of Lotronex® are not treated with the drug? If so, how are these patients to be identified?

      iii. assuring that Lotronex® is prescribed only to patients for whom it's indicated (e.g., women with a rigorously-established diagnosis of diarrhea-

predominant IBS? women in whom organic etiologies for symptoms have specifically been excluded?)

iv. assuring that only certain physicians with special knowledge of the benefits and risks of Lotronex® and of IBS be allowed to prescribe the drug? If so, how are these physicians to be identified?

v. maintaining the incidence of these toxicities at, or below, a certain level? If so, what are acceptable levels?

b. At this time, are there other appropriate goals of a risk-management program for Lotronex®?

c. Discuss specific criteria (e.g., outcome measures, endpoints) that should be measured to characterize the success of a risk management program for Lotronex®.

d. Discuss when in the risk management program for Lotronex® these specific outcome measures should be assessed.

2. **Interventions in the risk-management program for Lotronex®**

a. Please discuss which risk-management tools should be used to reduce risk and to achieve the desired goals and outcomes for a risk-management program for Lotronex®. As outlined in this package, various tools can be used to manage risk. Tools that could be used include, but are not limited to, product labeling (e.g., boxed warnings), special education programs, distribution of a Medication Guide (i.e., information required to be distributed to patients to educate them about Lotronex®'s benefits and risks, and on how to recognize these risks when prescribed the drug), special epidemiologic studies or clinical trials (please discuss controls, patient inclusion criteria, endpoints), and limiting distribution of Lotronex® to certain patients or physicians.

b. Please discuss which risk-management tools should be used to improve the benefit component of the benefit-risk balance for Lotronex® (e.g., taking steps to ensure that Lotronex® is used only in appropriate patients).

3. **Assessing the impact of risk-management interventions that are employed for Lotronex®**

The risk-management interventions for Lotronex® can be evaluated to determine whether they are having the desired impact. Such evaluations can be used to tailor the risk-management program to achieve the desired goals or clinical outcomes. Please provide

guidance on how best to evaluate whether the risk-management interventions implemented for Lotronex® are having their desired impact.

4. **Specifying next steps if the risk-management program for Lotronex® does not meet desired goals**

When interventions to optimize the benefit-risk balance for Lotronex® are initiated, these interventions may not yield the desired clinical outcome. For example, healthcare professionals or patients may not adhere to guidelines once they are implemented. Similarly, increased knowledge about the benefits and risks of Lotronex® may not translate into altered behaviors by healthcare professionals (e.g., prescribing patterns) or patients (e.g., following instructions in patient labeling).

a. Please discuss what additional steps should be followed if the goals or outcomes of a risk management program for Lotronex® are not being realized (as assessed by prespecified outcome measures).

b. Please comment on when (e.g., at what thresholds) you would consider using additional risk management interventions and specify what interventions should then be employed. For example, a threshold could be established for the degree of noncompliance with labeled contraindications. Similarly, thresholds could be established for rates of particular adverse outcomes (e.g., surgery, colostomy, death).