OVERVIEW AND RISK-MANAGEMENT ISSUES FOR LOTRONEX™ TABLETS

FDA Gastrointestinal Drugs Advisory Committee
27 June 2000

Discussion items

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. IBS is a condition that in itself does not threaten the lives of those affected. Lotronex™ is a palliative (not curative) treatment that diminishes the symptoms of IBS in some women. Prior to the drug's approval, the FDA Gastrointestinal Drugs Advisory Committee met on 16 November 1999 and discussed Lotronex™'s effectiveness and safety. During the meeting, the committee unanimously voted to recommend approval. At the time of the meeting, adverse events of ischemic colitis (in 3 of 900 patients, 0 on placebo), constipation (in 25-30% of patients receiving the drug compared to 5% with placebo), and one case of hepatotoxicity (in the Lotronex™ treatment group) were presented. Discussion focused on new data presented by Glaxo Wellcome implicating infection as the origin of the colitis rather than ischemia, the non-injurious but frequent nature of constipation, and the dispute over whether the case of hepatotoxicity resolved while on drug or off drug. The committee recommended post-marketing surveillance of adverse events and independent review of the pathology from patients with colitis. This independent review concluded three of four cases were consistent with ischemic colitis. In addition, upon review of records, the case of hepatotoxicity did, in fact, resolve after Lotronex™ was discontinued suggesting an association between the drug and this adverse effect.

Since Lotronex™ was approved, serious adverse events (including surgical complications of constipation, ischemic colitis, and liver toxicity) have been reported to the FDA in patients taking the drug. These reports support the drug's association with ischemic colitis, strengthen the estimated incidence rate for ischemic colitis of 1/100 to 1/1000, and raise continued concern about hepatotoxicity and new concerns about the sequelae of constipation.

FDA is convening this meeting of the Gastrointestinal Drugs Advisory Committee to review the benefit-risk profile for Lotronex™ to consider methods by which this profile can be optimized. In addition to seeking input on the specific risk-management plan proposed by Glaxo Wellcome, Inc., FDA will be seeking input in the following general areas:

- Discuss the specific safety goals and outcomes the committee 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 further dissemination of this new information (if so how broadly); or is the most appropriate goal that of assuring certain patients at high risk for the various toxicities are not treated with the product (if so, how are these people to be identified); or is the most appropriate goal that of assuring that only certain physicians with special knowledge of the benefits and

risks of this product be allowed to prescribe the product (if so, how are these physicians to be identified), or is the most appropriate goal that maintaining the incidence of these toxicities at or below a certain level (if so, what is that acceptable level)? Or is there some other more appropriate goal of a risk management program for this product at this time?

- Discuss the committee's perspectives on which risk-management tools should be used 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, the following items: a) product labeling, b) additional education of healthcare providers about the benefits, risks, and appropriate use of Lotronex™, c) distribution of a medication guide (i.e., labeling required to be distributed to patients) to educate patients about Lotronex™'s benefits and risks, and on how to recognize these risks when prescribed the drug, d) undertaking special epidemiologic studies, e) restricting distribution of the product to certain patients or to prescription by certain prescribers.

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

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

- 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 these outcome measures). For example, comment on when you would consider using additional risk management interventions and what interventions should be used.

- Comment on what steps could be taken 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).

Overview of benefit-risk reevaluations for marketed drugs

Whenever a newly established or suspected major safety problem is identified for a marketed drug, a reevaluation of the benefit-risk balance for that drug may be needed. The *Report of CIOMS Working Group IV* provides a framework for such a reevaluation of the benefit-risk balance of a marketed drug.[1] The report states that although most safety signals will not require the formal benefit-risk reevaluation proposed by the Working Group, the concepts are regarded

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[1] See *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals.* Report of CIOMS Working Group IV. Council for International Organizations of Medical Sciences (CIOMS), Geneva, 1998. A summary of the Working Group's proposals may be found in Chapter V of the report (pages 83-95). This report was distributed under separate cover to members and guests of the Gastrointestinal Drugs Advisory Committee.

as generally useful in any periodic or special evaluation of relative benefit and risks (page 11). The major components of the benefit-risk reevaluation proposed by the Working Group are (1) an evaluation of benefits, (2) an evaluation of risks, (3) a comparative evaluation of benefits and risks, (4) an analysis of appropriate options for action, and (5) decision-making (i.e., selection and implementation of one or more of the identified options).

This meeting of the Gastrointestinal Drugs Advisory Committee brings experts, stakeholders, and other constituencies together in a public forum to discuss current evaluations of safety signals for Lotronex™. At this meeting, FDA seeks input from the Advisory Committee on risk-management strategies that could be implemented for Lotronex™ Tablets. Moreover, FDA seeks input on how the success of risk-management interventions for Lotronex™ Tablets might be evaluated.

Irritable bowel syndrome

Irritable bowel syndrome is a functional gastrointestinal disorder characterized by manifestations that include abdominal pain (or abdominal discomfort) and altered bowel habits such as altered stool frequency, form, or passage.[2] Some patients experience abdominal bloating or distention. The severity of IBS symptoms varies from patient to patient. In some individuals afflicted with IBS, symptoms may be incapacitating. IBS, however, is a condition that does not increase susceptibility to other chronic gastrointestinal diseases (such as colon cancer or inflammatory bowel disease), directly result in serious health sequelae, or threaten the lives of those affected.

IBS is classified as a functional bowel disorder because structural or biochemical abnormalities that consistently are associated with the condition have not been identified. The diagnosis is made clinically, such as by application of the clinical criteria established by Manning and co-workers, and after other diagnoses have been excluded. Estimates of the prevalence of IBS in the United States vary widely, and 10-22% of adults have symptoms compatible with the disorder. Among IBS patients seen by physicians, women outnumber men by a ratio of about 2:1. Of these women, a sizeable proportion have diarrhea-predominant IBS. Thus, the pool of patients who might be prescribed Lotronex™ for its labeled indication is substantial.

The treatment of IBS requires a comprehensive approach to the patient. Treatment options include dietary modifications, and drug treatment (e.g., antispasmodics, anticholinergics, antidepressants, prokinetics, narcotics),

Lotronex™ (alosetron hydrochloride) Tablets

Lotronex™ was approved for marketing by FDA on 9 February 2000 for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea. The application for Lotronex™ had been given a priority 6-month review by FDA, and it was

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[2] See Appendix 1 (cumulative pages 30-58) for additional background information on irritable bowel syndrome.

discussed by FDA's Gastrointestinal Drug Advisory Committee on 16 November 1999.[3] The active ingredient in Lotronex™ is alosetron hydrochloride, an antagonist at 5-hydroxytryptamine type-3 ($5\text{-}HT_3$) receptors. The recommended adult dosage of Lotronex™ is 1 mg taken orally twice daily, with or without food.

Lotronex™ was the first drug approved in many years (e.g., decades) specifically for the treatment of IBS. As such, its approval was likely to have been anticipated by patients and their families as well as by healthcare professionals who treat patients with the disorder. Lotronex™, however, is a palliative (not curative) symptomatic treatment of IBS and is a treatment that has not been shown to prevent the progression of IBS symptoms.

Efficacy of Lotronex™: Risk-benefit issues

Although the primary focus of this Advisory Committee meeting is on safety information and risk management for Lotronex™ Tablets, a brief summary of the efficacy issues is relevant. Lotronex™ has been shown to be effective in women with IBS whose predominant bowel symptom is diarrhea.[4]

Identifying the target population: Lotronex™ has been shown to be effective in women with IBS whose predominant bowel symptom is diarrhea. Lotronex™ has not been shown to be effective in men, pediatric patients, or in women with IBS whose bowel symptoms alternate between diarrhea and constipation. Women with IBS whose predominant bowel symptom is constipation represented a small fraction of women studied, and safety considerations preclude the use of Lotronex™ in constipated patients (see below). To increase the effective use of the drug, Lotronex™ should be administered to women who have a legitimate diagnosis of IBS (e.g., not a misdiagnosis or a casual diagnosis of IBS) and who have diarrhea as their predominant bowel symptom.

Identifying responders: In the subset of women with diarrhea-predominant IBS, improvement attributable to Lotronex™ occurred only in a relatively small percentage of patients (e.g., 10-20%).[5] Of the remaining women with diarrhea-predominant IBS, approximately 40% failed to improve, and 40-50% improved spontaneously or due to other factors (e.g., a placebo effect). These clinical trial data may be used to anticipate efficacy during actual use of the marketed product in women with diarrhea-predominant IBS. These data predict that in women with diarrhea-predominant IBS who take Lotronex™ *and improve*, the improvement will be spontaneous (or due to other factors not attributable to Lotronex™) in approximately 70-80% of those women. That is, patients with spontaneous improvement will be exposed to the risks of

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[3] Transcripts from the FDA Gastrointestinal Drugs Advisory Committee Meeting held on November 16, 1999 have been distributed under separate cover.

[4] See FDA Review #1 (cumulative pages 170-182) in Appendix 2.

[5] As assessed by the primary endpoint over three months in the principal efficacy studies. See Tables 4 and 5 in FDA Review #1 in Appendix 2 (on cumulative pages 180-181).

Lotronex™ without benefit. Moreover, these patients may continue to take Lotronex™ because they believe their improvement is due to the drug, when in fact their improvement is due to other factors. To increase the effective use of the drug, Lotronex™ should be continued in women who have improvement that is attributable to the drug (if it is possible to identify such women). Such patients would experience benefit as well as risk from use of the drug.

Other populations: Lotronex™ has not been shown to be effective in men or in pediatric patients. In men, a phase-2 dose-ranging study (S3BA2001) did not provide evidence that the drug was effective compared to placebo, even at a dosage eight times the dosage approved for women (8 mg b.i.d. vs. 1 mg b.i.d., respectively). Approximately 110 men, distributed over five dose groups (placebo, and Lotronex™ 1, 2, 4, or 8 mg b.i.d.), were enrolled in this study. Consequently, Glaxo Wellcome did not pursue evaluation of efficacy of the drug in men in subsequent efficacy studies.

Safety of Lotronex™: Risk-benefit issues

Since Lotronex™ was approved for marketing on 9 February 2000, new gastrointestinal serious adverse events have been reported to the FDA in patients taking the drug. These adverse events include constipation (with surgical complications), ischemic colitis, and liver toxicity. These new data raise additional safety concerns about Lotronex™ because they include patients who have suffered worse clinical outcomes than patients treated previously with the drug. Moreover, these new data raise additional safety concerns about Lotronex™ because they more strongly implicate Lotronex™ as being causally associated with these serious adverse events. In the following summary, 1 June 2000 is used as the cut off date for serious adverse events. See Tab 2 (cumulative pages 8-12 of this package) for more information about these adverse events.[6]

Constipation: Overall, seven cases of constipation have been reported to FDA as serious adverse events among patients taking Lotronex™. Six of these patients were hospitalized and three underwent surgery.

Prior to approval, constipation was identified in both sexes as a frequent side effect caused by Lotronex™. In clinical studies 25-30% of patients receiving Lotronex™ experienced constipation. The frequency of constipation increased with the dose of the drug. At the recommended dosage (1 mg b.i.d.), the frequency of constipation was significantly greater in patients receiving Lotronex™ than in those receiving placebo (27% of 702 patients vs. 5% of 834 patients, respectively). About 10% of patients who received Lotronex™ twice daily could not tolerate the constipation and had to discontinue therapy with Lotronex™ permanently. Approximately 9% of patients receiving Lotronex™ discontinued therapy with the drug for a few days because of constipation, but then were able to continue therapy. Prior to approval, no serious adverse events related to constipation were reported to FDA.

Since approval, however, seven serious adverse events related to constipation have been reported

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[6] See Appendix 1, cumulative pages 59-160, for general background information on constipation, ischemic colitis, and drug-induced hepatotoxicity.

to FDA. Six of these patients were hospitalized, and three of these patients required surgery. Of the three patients that required surgery, one patient required a total colectomy and an ileostomy for gangrenous colitis and toxic megacolon. A second patient required surgical repair and antibiotics for perforation of the sigmoid colon and an abscess. A third patient needed a temporary colostomy for decompression of intestinal obstruction of the small bowel.

Ischemic colitis: Overall, twelve cases of ischemic colitis have been reported to FDA as serious adverse events among patients taking Lotronex™. Eight of these patients were hospitalized. The remaining four patients, although not hospitalized, had symptoms severe enough to require endoscopy. None of these patients required surgery. These cases may represent a new variety of nonthrombotic ischemic colitis. The rate of ischemic colitis in post-marketing experience appears to be very similar to the rate seen in clinical trials: preliminary point-estimates for these rates range from about 1/700 to about 1/900 patients (treated with Lotronex™).

Prior to approval, ischemic colitis was diagnosed in four patients receiving Lotronex™. Each case resolved after discontinuation of Lotronex™. These cases were discussed at the meeting of the Gastrointestinal Drugs Advisory Committee on 16 November 1999. At that meeting, Glaxo Wellcome, Inc. provided new data that suggested that some of these cases may have been of infectious etiology. The company supported this argument, in part, by providing the results of immunohistochemical staining for E. Coli O157:H7 that had been performed on tissue sections from the affected patients. However, a review of these biopsy sections by independent pathologists at the request of FDA (and as recommended by the Gastrointestinal Drugs Advisory Committee of 16 November 1999) indicated that three of the four cases were consistent with the diagnosis of ischemic colitis; no specific lesions were noted in the fourth case. The immunoperoxidase stain available on three cases was interpreted as negative in each case. The cases that had cultures obtained during patient presentation were also negative. See FDA review #1 in Appendix 2 (cumulative pages 191-208 of this package) for a review of these cases.

At the time of approval, whether Lotronex™ caused these cases of ischemic colitis was uncertain although the clinical trials database presented a signal for toxicity. Since approval, however, an additional eight cases of ischemic colitis have been reported to FDA in patients taking Lotronex™. Four of these patients were hospitalized. The remaining four patients, although not hospitalized, had symptoms severe enough to require diagnostic endoscopy. None of these patients required surgery.

Hepatotoxicity: Overall, three cases of hepatotoxicity have been reported to FDA as serious adverse events in patients taking Lotronex™-- one during drug development and two post-approval. Maximum ALT elevation in the pre-market case was 131 IU/L (normal range 6-34 IU/L); total bilirubin reached 2.1 mg/dL (normal range 0.2-1.2 mg/dL). The patient was hospitalized following ERCP to evaluate the elevated liver function (LFT) tests. LFTs returned to normal after stopping Lotronex™. The two cases of hepatotoxicity reported post-approval were both hospitalized. One of the patients, for whom maximum reported ALT elevation was 891 IU/L, was taking multiple concomitant medications. LFTs returned to normal on withdrawal of Lotronex™ and mitrazapine. In the second post-approval case reported ALT levels rose to a maximum of 210 IU/L. LFTs returned to normal after the patient stopped taking Lotronex™. Total bilirubin was not available for either of these two cases.

Risk management options

Several options are available to manage the risks associated with use of Lotronex™. Different risk-management options can be used together to increase the overall effectiveness of the risk-management program. See Tab 3 (cumulative pages 13-17) for a general discussion for six risk-management options:

(1) Labeling for prescription drugs must bear adequate directions for use, including information about risks. Labeling of prescription drugs includes information for healthcare professionals as well as for patients. For example, a Medication Guide is an information leaflet, required by regulation, to be distributed to patients when a prescription drug is dispensed. A Medication Guide is written in lay language and is intended to inform patients about the benefits, risks, and use of a particular prescription drug. It educates patients on how to recognize specific risks associated with that drug. See Tab 3 for a discussion of labeling options and Appendix 4a for examples of labeling options (e.g., Boxed Warnings, Patient Package Inserts, Medication Guides). FDA can require a medication guide in a few drugs per year where the agency determines that patient education and knowledge will play a major role in risk management.

(2) Communications and educational programs may be used to inform healthcare practitioners and consumers about the risks and benefits of a drug, including information on how the drug is intended to be used (or not used), and for whom the drug is intended (or not intended) to be used. For example, a "Dear Healthcare Provider" letter may be used to educate healthcare professionals, and educational programs can be targeted toward patients and patient advocacy groups. See Tab 3 for a discussion of different types of communication, and Appendix 4b for examples of these communication options (e.g., Dear Healthcare Provider letters, Talk Papers, Public Health Advisories, Questions and Answers, List of MedWatch partners).

(3) Advertising for prescription drugs must present a fair balance of benefit and risk information. Advertising is an activity that may be directed toward healthcare professionals or consumers. Advertising directed toward healthcare professionals may be designed to ensure that a drug is used only by appropriately trained clinicians or in specific clinical settings. See Tab 3 for a discussion of advertising, and Appendix 4c for guidances and regulations pertinent to advertising for prescription drugs.

(4) Packaging for drugs may be used to manage risk. For example, unit-of-use packaging can be used in conjunction with a Medication Guide to ensure that patients who are dispensed a prescription drug receive important information about that drug. See Tab 3 for a discussion of packaging.

(5) Restricted distribution may be either voluntary or required by regulation. For example, restricted distribution may be used to ensure that a drug is used only by appropriately trained clinicians (e.g., by clinicians trained to diagnose a particular condition, by clinicians trained to recognize or to manage particular adverse events) or distributed to specific health care facilities. See Tab 3 for a discussion of restricted distribution and

Appendix 4d for background materials on accelerated approval.

(6) Cessation of marketing may be voluntary. FDA also may initiate proceedings to withdraw the approval of a drug. See Tab 3 for a discussion of drug withdrawal and Appendix 4e for related regulations.

Evaluation of risk-management interventions

Although interventions to improve the benefit-risk balance for Lotronex™ may be initiated, these interventions may not be effective in achieving the desired clinical outcome. For example, healthcare professionals may not adhere to guidelines once they are implemented for a variety of reasons. Background information on risk communication, adherence to guidelines, and other aspects of improving the benefit-risk balance of drugs may be found in Appendix 5.

Thus, interventions designed to improve the benefit-risk balance should 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 clinical outcomes. See Tab 4 (cumulative pages 18-29) for an overview of risk interventions and their evaluation, including two case studies.