



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Sidney M. Wolfe, M.D.
Elizabeth Barbehenn, Ph.D.
Public Citizen's Health Research Group
1600 20th Street, NW
Washington, DC 20009-1001

Re: Docket No. 00P-1499/CP1

Dear Drs. Wolfe and Barbehenn:

This letter responds to your citizen petition dated August 31, 2000 (petition), and supplement dated October 30, 2000 (supplement), asking the Food and Drug Administration (FDA) to immediately remove from the market Lotronex (alosetron hydrochloride) because of multiple instances of adverse events associated with the drug.

On June 7, 2002, FDA approved a supplemental new drug application (sNDA) from GlaxoSmithKline (GSK) under 21 CFR 314, subpart H, that permits marketing of Lotronex with restrictions. Your petition is granted in part because under the terms of the sNDA (including the Lotronex Risk Management Program and significant labeling changes), the safety issues raised in your petition have been addressed. Your petition is also denied in part because we decline to remove Lotronex from the market, as its use is generally limited to a patient subpopulation for whom the benefits of using the drug outweigh the risks.

Since your petition was filed, FDA has addressed a number of concerns about the risks and benefits of Lotronex that were cited. For example, the data considered for the sNDA were not available at the time the petition was filed. Additionally, the Risk Management Program (discussed in section II.E. of this document), a critical element in the sNDA approval, was not initiated at the time the petition was filed. As discussed in section II.C. of this document, we find that as used for the subpopulation of Irritable Bowel Syndrome (IBS) sufferers for whom it is now indicated, the benefits of Lotronex outweigh the risks. In addition, the Risk Management Program specifically addresses your concerns about use of the drug by poorly monitored individuals (Petition at 8). It is anticipated that under the Risk Management Program, adverse events, while not eliminated, will significantly decrease.¹

¹ You also state that Lotronex is a "minimally effective drug" whose occurrence of serious adverse reactions tips the risk-benefit equation against using the drug (Petition at 1) and that then-proposed labeling changes and Medication Guide issuance are inadequate to protect patients (Petition at 8). As discussed in section II of this document, data assessed since the petition was filed indicate that Lotronex is, in fact, effective for a patient subpopulation for whom the benefits of using the drug outweigh the risks. In addition, the Medication Guide has been revised to reflect new labeling that we believe is now adequate to protect patients.

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We further believe that the labeling changes approved as part of the sNDA, revised Medication Guide, and Risk Management Program adequately inform and protect patients with regard to the risks and benefits of Lotronex.

I. BACKGROUND

A. Initial Approval

Lotronex, manufactured by GlaxoSmithKline (GSK), formerly Glaxo Wellcome, was initially approved on February 9, 2000, for treatment of women with IBS whose predominant bowel symptom was diarrhea.² Data supporting the efficacy of Lotronex were provided by two multicenter, randomized, double-blind, placebo-controlled trials in women with nonconstipated IBS. The primary efficacy results in the overall study samples demonstrated effectiveness, but the efficacy of Lotronex was largely limited to the subgroup of women with diarrhea-predominant IBS (IBS-d). The therapeutic gain (Lotronex over placebo) of the percentage of monthly responders in women with diarrhea-predominant IBS ranged from 10 to 19 percent. Effects of Lotronex on secondary outcome variables (e.g., bowel urgency, stool consistency, and stool frequency) were consistent with the primary efficacy results.

Two major adverse events were noted in the clinical trials for Lotronex: dose-related constipation and ischemic colitis. No patients with constipation experienced serious complications. Four patients were reported to have experienced transient, self-limited ischemic colitis. These events were assessed as being self-limited and reversible upon discontinuation of Lotronex. No deaths occurred in patients receiving Lotronex.

B. Postmarketing Experience

After GSK started marketing Lotronex, FDA began receiving reports of serious complications of constipation and cases of ischemic colitis, some severe, associated with use of the drug. By June 2000, FDA had received seven reports of serious complications of constipation, three of which required surgical intervention. In addition, twelve new cases of ischemic colitis, some severe, were reported, none of which required surgery. No deaths were reported.

As a result of the increasing seriousness of postmarketing reports of gastrointestinal adverse events, FDA and GSK initiated several risk-management interventions designed to reduce the incidence of serious adverse events associated with the use of Lotronex. These included adding a Black Box Warning to the labeling and the issuance of a Medication Guide to educate patients about potential adverse events.

² Note that the current indication is for women with *severe* diarrhea-predominant IBS.

In September and October 2000, FDA received the first reports of death and ischemic colitis leading to surgical complications associated with the use of Lotronex.

C. Withdrawal from Marketing

On November 28, 2000, FDA met with GSK and proposed three possible options: (1) a voluntary withdrawal of Lotronex from the market with limited access under an investigational new drug application (IND), (2) temporary suspension of drug marketing pending a public advisory committee discussion of scientific issues related to the safe use of Lotronex, or (3) restricted distribution to patients currently receiving Lotronex who sign an informed consent form. After considering these options, Glaxo Wellcome voluntarily withdrew Lotronex from the market, notifying the Agency on December 1, 2000, that it had ceased all sales and distribution.

D. Post-Withdrawal

Following the withdrawal of Lotronex from the market, many patients contacted FDA seeking access to the drug.³ The patients described their suffering from the chronic and disabling nature of their IBS symptoms and expressed frustration with their inability to successfully control their IBS symptoms with therapies other than Lotronex.

During this time, FDA and GSK had many communications about the possible options for making Lotronex available to appropriate IBS patients. While GSK declined to make Lotronex available to patients under an IND, the company said it was willing to market the drug under restricted conditions.

E. The Advisory Committee Hearing

On April 23, 2002, FDA held a joint meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Subcommittee to discuss the risk-benefit profile of Lotronex to assist FDA in determining whether Lotronex should be returned to the market and, if so, under what conditions.⁴ The Advisory Committee members voted 16 to 2 in favor of reintroducing Lotronex under a restricted distribution system, urging identification of the subgroup of IBS patients for whom Lotronex is most effective.

Following FDA agreement with GSK on the details of the Lotronex Risk Management Program and other labeling issues (described in sections II.A. and II.C. of this document), an sNDA was approved on June 7, 2002.

³ On April 9, 2001, the Lotronex Action Group, a patient advocacy group, submitted a citizen petition (Docket No. 01P-0169/CP1) to FDA requesting that Lotronex be returned to the market.

⁴ Transcript available on the Internet at <http://fda.gov/ohrms/dockets/ac/02/transcripts/3848T1.htm>.

II. FDA'S BASIS FOR APPROVING THE LOTRONEX sNDA AND ALLOWING ITS REINTRODUCTION

Since the withdrawal of Lotronex, substantial amounts of new information about the drug have become available, including data from clinical trials that were ongoing (and then terminated) at the time the drug was withdrawn. This additional randomized clinical trial experience gave FDA a broader scientific foundation upon which to base its regulatory actions on Lotronex.

Based on retrospective and prospective analyses, we conclude that Lotronex is an effective medication for severe IBS-d.⁵ We further conclude that the safety issues that arose with the use of Lotronex at the time the petition was submitted occurred primarily because its approved indication was too broad and the drug was sometimes used in inappropriate situations (such as for non-IBS patients for diarrhea control).

Under the terms of the sNDA approval, we believe that the narrowed indication and components of the Risk Management Program (prescribing program, adverse event collection, physician/patient/pharmacist education, program evaluation, and postmarketing commitments) significantly improve the safety profile of Lotronex so that the benefits of reintroduction outweigh the risks. Exposure is now limited to a smaller population whose IBS-d is disabling and unresponsive to other therapies, and who may experience benefit. The Risk Management Program is designed to reduce uses of Lotronex in casual and inappropriate circumstances. The educational component of the Risk Management Program will help ensure prescribers and patients are well aware of the risks and the effectiveness of the drug.

A. Efficacy

Studies indicate that patients on Lotronex had significant increases over placebo (13 to 16 percent) in terms of days with urgency control. In studies where the end point was urgency less than 1 day a week compared to 5 days a week at study commencement, 32 percent of patients on Lotronex compared to 19 percent on placebo met this end point. In two other studies, 50 percent of patients on Lotronex compared to 29 percent of patients on placebo met this end point. Thus, in these groups of patients with the potential for large improvements in urgency, substantial numbers had improvements.

⁵ We considered but rejected limiting reintroduction to IND access because we believe that each of the relevant controls associated with IND access is addressed by the Risk Management Program, including informed consent (Patient-Physician Agreement), physicians having appropriate qualifications (Physician Attestation), reporting of adverse events (responsibilities under Physician Attestation and a GSK agreement to report serious adverse events within 15 days of receipt), and periodic contact with a health care provider (prescriptions with affixed stickers must be used to obtain drug, requiring contact with the prescribing office).

In summary, Lotronex has shown beneficial effects on several symptoms of IBS, and some patients with severe symptoms (e.g., urgency) have a large benefit. Patients less likely to benefit from Lotronex are those with stool consistency that is hard or lumpy or those with a stool frequency of less than two per day.

B. Safety Assessment

We performed a multidisciplinary review of the safety of Lotronex, centering its reviews on analyses of selected serious (or potentially serious) adverse events, including ischemic colitis, mesenteric ischemia/infarction, serious complications of constipation, and death. We evaluated data from the randomized clinical trials as well as from postmarketing reports received through October 2003.

We focused on three main areas concerning the risk of serious adverse events (particularly the risk of ischemic colitis): (1) risk quantification, (2) whether the risk changes over time, and (3) whether subsets of patients at greater or lesser risk can be identified.

As of March 8, 2002,⁶ there were 84 cases of ischemic colitis and 113 cases of serious complications of constipation reported to FDA through the Adverse Event Reporting System (AERS). In IBS clinical trials, the incidence of serious complications of constipation in women was approximately 1 per 1,000 patients, but approximately 10 percent of patients on Lotronex withdrew prematurely because of constipation. The cumulative incidence of ischemic colitis in women receiving Lotronex was 2 per 1,000 patients (95% confidence interval 1 to 3) over 3 months and was 3 per 1,000 patients (95% confidence interval 1 to 4) over 6 months. Patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking Lotronex for longer than 6 months.

The quantitative risks of ischemic colitis are expressed in the product labeling in a way that can be understood by health care providers and patients. (See current product labeling contained in the sNDA approval letter, attached).

Since reintroduction into the market on November 20, 2002, the use of Lotronex is restricted to physicians who enroll in the Risk Management Program. Between November 30, 2002, and October 30, 2003, there were four reported new cases of ischemic colitis. None of these cases required surgical intervention, and there were no ischemic colitis related deaths as of October 30, 2003.

Constipation is a dose-related side effect of Lotronex, occurring in approximately 30 percent of patients receiving Lotronex at a dose of 1 milligram BID in clinical trials (compared with about 5% receiving placebo). The dose-related nature of Lotronex-induced constipation is reflected in current product labeling. Since reintroduction into

⁶ Our postmarketing database was "frozen" on this date to prepare for data analysis at the Advisory Committee hearing on April 23, 2002. More recent data is discussed below.

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the market, as of October 30, 2003, four reported cases of serious complications of constipation (SCC) have been identified. The case definition for SCC was constipation or suspected constipation that led to an emergency room visit, hospitalization, or complications, including but not limited to, fecal impaction, bowel obstruction, necrosis, or rupture. Of the four cases of SCC, two patients required hospitalization and one patient required laparoscopy.

To summarize, we find that approving the sNDA for Lotronex will allow patients with the most disabling symptoms, and who have the most to benefit from the use of Lotronex, access to the drug when the patients and their physicians agree the benefits of the drug exceed risks.

C. New Labeling

The label contains several important revisions that, combined with the accompanying Risk Management Program, makes Lotronex safer to use. Approved labeling includes the Package Insert, the Medication Guide, the Patient-Physician Agreement, and the Physician Attestation. To improve readability, we approved short, concise boxed warning statements, careful use of bolding, and less repetition.

Lotronex is now indicated only for women with severe diarrhea-predominant IBS who have:

- Chronic IBS symptoms (generally lasting 6 months or longer)
- Had anatomic or biochemical abnormalities of the gastrointestinal tract excluded
- 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

The new indication aims to clarify for physicians the intended population for Lotronex use.

Chronic IBS is defined as greater than 6 months. IBS of shorter duration could be a symptom of another disease that is not fully manifested.

Diarrhea-predominant IBS is also defined in the indications section to guide physicians on what patients can appropriately be prescribed Lotronex. As there is no agreed upon definition of mild, moderate, or severe IBS, the components of *severe* IBS-d were agreed upon with GSK from patient descriptions of disabling IBS-d. The label states less than 5

percent of IBS is severe. This statement is included to help physicians realize that it is the uncommon patient who would be considered for Lotronex.

The clinical trials section deletes much of the previous description of the effects of Lotronex in the pivotal trials population, because that population is no longer relevant for Lotronex's new, limited indication. That population included a variety of types of IBS that were nonconstipating. The new clinical trials section includes retrospective analyses done on patients who had indicated their symptoms were severe. The clinical trials section also includes new data from patients with moderate to severe urgency studied with Lotronex. Prospective data and retrospective data from these trials demonstrate efficacy in women with severe IBS-d.

D. Postmarketing Commitments

GSK's agreement to conduct postmarketing studies was also a significant factor in our allowing the reintroduction of Lotronex. Two of the studies relate to evaluation of the Risk Management Program described in section II.E. Another study estimates whether Lotronex is being prescribed by unenrolled physicians and whether these prescriptions are being filled. Finally, two additional studies investigate efficacy of lower doses of Lotronex that may have fewer side effects of constipation and evaluate safety and efficacy of "as needed (prn)" usage of Lotronex.

As part of their postmarketing commitment, GSK has agreed to report serious adverse events and death to FDA within 15 days. GSK and FDA will also be meeting quarterly for the first year to review the Risk Management Program.

E. Risk Management Program

The goals of the Risk Management Program are to:

- Limit use of Lotronex to a subpopulation of patients in whom the benefits exceed the risks
- Inform patients and physicians of the risks and benefits of Lotronex so that they can make an informed decision about using the drug
- Limit use of the drug to physicians who can manage severe IBS-d patients and the adverse events associated with Lotronex and who agree to accept certain responsibilities under the program such as reporting adverse events
- Have an ongoing program evaluation to ensure goals are met. Because IBS-d is a symptomatic disease, if Lotronex is not working adequately for the patient, the patient can stop the drug and eliminate risk of Lotronex-induced adverse events.

Briefly, the Lotronex Risk Management Program includes each of the following components:

- Enrollment of qualified physicians in a physician prescribing program

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- Implementation of a program to educate physicians, pharmacists, and patients about the risks and benefits of Lotronex
- 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)
- Implementation of a plan to evaluate the effectiveness of the program

Complete details about the Risk Management Program are available on the Internet at <http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm>. A copy of the sNDA approval letter describing the program is enclosed.

III. CONCLUSION

We believe that the benefits of reintroducing Lotronex with a narrowed indication for women with severe diarrhea-predominant IBS outweigh the risks, given the approved labeling changes and Risk Management Program.

We appreciate the valuable input you've provided throughout this process, and we encourage your continued communication with us with regard to the ongoing Lotronex Risk Management Program.

Sincerely,



Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research

Attachment