Update on Risk Management Activities for Lotronex (alosetron hydrochloride)

Executive Summary

GlaxoSmithKline (GSK), manufacturer of Lotronex, and the Food and Drug Administration's Division of Gastrointestinal and Coagulation Drug Products are providing the Drug Safety and Risk Management Advisory Committee an update on the status of the risk management plan (RMP). Both GSK and FDA view the RMP as satisfactorily meeting the goals of:

1. limiting use to a subpopulation of patients in whom the benefits exceed risks
2. informing patients and physicians of the risks and benefits of Lotronex so that they can make informed decisions
3. limiting use of the drug to physicians who can manage severe diarrhea-predominant irritable bowel syndrome and adverse events associated with Lotronex (ischemic colitis and severe complications of constipation)
4. having an on-going program evaluation to ensure goals are met

This briefing package contains:

1. Background and summary of risk management plan
2. Summary of outcomes under the risk management plan.
3. FDA summary of adverse events.
4. The FDA approval letter dated June 7, 2002 that provides for the risk management plan for Lotronex and the approved labeling.
5. Office of Drug Safety Postmarketing Safety Review of April 1, 2004

Background and Summary of Risk Management Plan

Lotronex is a 5-HT_3 serotonin receptor antagonist. It inhibits activation of non-selective cation channels which results in the modulation of the enteric nervous system and affects pain and discomfort and gastrointestinal transit in patients with diarrhea-predominant irritable bowel syndrome (IBS). It was first approved with warnings for ischemic colitis in February, 2000. However, after a few short months of marketing FDA received about a dozen cases of ischemic colitis and serious consequences of severe constipation. The June 27, 2000 Gastrointestinal Drugs Advisory Committee recommended labeling and education for safe use. However, by November 28, 2000, the manufacturer voluntarily withdrew the drug from marketing when more cases, including fatalities, were received. After withdrawal, the FDA heard from hundreds of patients urging access to Lotronex. GSK agreed to pursue re-marketing of Lotronex under restrictions.

On April 23, 2002, the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee met and recommended approval of Lotronex Tablets with restrictions, such as having patient and physician registries and physician certification training for prescribing. On June 7, 2002, the U.S. Food and Drug

Administration (FDA) approved the restricted marketing of Lotronex with a risk management plan (RMP) which was mutually agreed upon by GlaxoSmithKline (GSK) and FDA. The approval and RMP provide for:

1. Revised labeling, including a Medication Guide, with lower dosing recommendations and a limited indication for women with severe diarrhea-predominant IBS who fail to respond to conventional therapy and have specified symptoms.
2. A prescribing program that enrolls prescribing physicians who meet the qualifications for diagnosing and managing IBS and drug adverse events (ischemic colitis and severe complications of constipation), and who agree to specific responsibilities. The program allows pharmacists to check if prescribers are enrolled. GSK has implemented a sticker system.
3. Adverse event reporting to FDA within 15 days of specified serious adverse events.
4. Risk management evaluation plans.
5. Postmarketing commitments to study
    a. Efficacy of lower doses
    b. "prn" dosing efficacy
    c. DNA analyses of subjects in a. and b. who develop ischemic colitis and to determine genotype polymorphic CYP enzymes responsible for Lotronex metabolism
    d. Mechanistic studies to explore Lotronex-induced ischemic colitis and small bowel ischemia
    e. Pharmacokinetic studies in hepatically-impaired subjects and drug-drug interaction studies with CYP inhibitors
    f. Prescribing of enrolled prescribers versus all Lotronex prescribers
    g. Compliance with Patient-Physician Agreements, appropriate use of Lotronex, knowledge and understanding of patients, serious adverse events to estimate rates, possible risk factors for serious gastrointestinal adverse events

Summary of Outcomes

Since marketing began on November 20, 2002, through December 2003 a total of 5,053 physicians have enrolled in the Prescribing Program for Lotronex (PPL) to prescribe Lotronex. The PPL is one of the key elements of the RMP for Lotronex. To enroll, physicians must attest to qualifications of being able to diagnose and manage IBS, ischemic colitis, and severe complications of constipation, as well as being knowledgeable about the drug's labeled information. The attestation must be submitted before prescribing materials, including prescription stickers for pharmacists to recognize the prescriber is enrolled, are sent. About 2,500 physicians (approximately 50% of enrolled physicians) have prescribed or currently are prescribing the drug. However, only about 20% of the enrolled physicians actually prescribed the drug in a given month. For the quarter, September-December 2003, about 60% of the enrolled physicians were gastroenterologists, 34% were primary care physicians and 5% were "other." From

month to month approximately 20% of all prescribers of Lotronex are not enrolled in the PPL (most are primary care physicians and family practitioners). Non-enrolled prescribing physicians are sent enrollment kits and informational letters in efforts to get them to enroll. Over time these interventions have resulted in approximately 75% of the non-enrolled prescribers either enrolling or ceasing to prescribe. Thus, the "20% group" constantly changes in membership as previous non-enrolled prescribers either enroll or cease to prescribe and "new" non-enrolled prescribers become a part of the group. Pharmacies in areas where non-enrolled prescribers practice, are sent information regarding the Prescribing Program for Lotronex. Whether patients managed by non-enrolled physicians are at a different risk for clinically serious outcomes is unknown. Over the same time period, November 2002 through December 2003, 9,365 patients were prescribed Lotronex at least once. This represents a small portion of potential patients. However, only 10-20% of these patients have had additional prescriptions of Lotronex. The reasons for this low rate of additional prescriptions are not yet known. In addition, patterns of usage (e.g., doses, drug holidays) need to be clarified.

As of December 31, 2003, approximately 36% of the total patients prescribed Lotronex had completed a questionnaire about patient knowledge of risks, most scoring 90% or higher for correctly answering questions about the risks of Lotronex. The generalizability of the results in this survey population to the larger group of all patients treated with Lotronex is unknown. Eighty percent (80%) of the patients eligible for Lotronex fulfilled all three severity criteria listed in the approved indication whereas, only one severity criterion is required, in addition to diarrhea. It should be noted that the percentage of patients with one of the listed criteria of severity that also report the other two is unknown.

FDA Report of Adverse Events

From November 20, 2002 until February 21, 2004, there have been 8 reported cases of ischemic colitis (3 requiring hospitalization, no surgeries) and 5 reported cases of severe complications of constipation (2 requiring hospitalization and 1 unconfirmed laparoscopy). There have been no drug-related deaths.

Conclusion

GSK has conducted focus testing to explore where there could be improvements in risk communication and enrollment procedures. FDA and GSK continue to review the RMP and outcomes to improve the program.