Questions for the Committee

Gastrointestinal Drugs Advisory Committee & Drug Safety and Risk Management Subcommittee of the Advisory Committee for Pharmaceutical Science

April 23, 2002

1. Can a patient population with diarrhea-predominant irritable bowel syndrome (IBS) be described for which the benefits of Lotronex™ outweigh the risks? If not, why not? If so, describe the population in terms of the following characteristics: severity of symptoms, degree of disability, chronicity of IBS, failure of conventional IBS therapies, and any other important characteristics.

2. At this time, should Lotronex be a) available to patients with diarrhea-predominant IBS without marketing restrictions, b) available to IBS patients with appropriate marketing restrictions (to be defined), or c) withheld from the market? Explain.

3. If Lotronex is marketed, should the ability to prescribe Lotronex be limited to certain types of physicians? If so, describe the physicians in terms of the following qualifications: knowledge, experience, specialty, and any other important characteristics.

4. Regarding **patients**:
   a. GlaxoSmithKline (GSK) proposes to restrict use of Lotronex to patients who sign a Patient-Physician Agreement. This agreement is then filed in the patient's medical record. Is this adequate to ensure that only patients with the most favorable benefit-risk balance receive Lotronex? Is auditing of this agreement needed?
   b. GSK proposes a utilization study of the UnitedHealthcare Research Database (UHC) as a mechanism to audit whether appropriate patients are being prescribed Lotronex. Is this auditing mechanism adequate to achieve the goal? If not, describe an adequate auditing mechanism.
   c. GSK proposes a pharmacy-based study using the Slone Epidemiology Unit and Eckerd Corporation to audit patients' knowledge and awareness of the risks and benefits of Lotronex. Is this auditing mechanism adequate to achieve the goal? If not, describe an adequate auditing mechanism. Define adequate performance on either GSK's or another knowledge audit.
   d. Should patient enrollment (e.g., registration) be part of the risk-management plan?

5. Regarding **physicians**:
   a. GSK proposes a plan in which physicians call a 1-800 number to receive a self-attestation kit, including stickers. The physicians self attest to their qualifications by signing the "Section for the Physician" on the Patient-Physician Agreement. This agreement is then filed in the patient's medical record. Is the sponsor's proposal adequate to allow for evaluation of physician adherence to the program (e.g., the extent of Lotronex prescribing outside of the program)? If not, describe an adequate auditing mechanism.
   b. Define an adequate level of adherence to the program by physicians.
   c. Should physician enrollment (e.g., registration) be part of the risk-management plan?

6. Regarding **pharmacists**:
   GSK proposes that pharmacists accept only written prescriptions with an attached sticker. The goal is to verify in real-time that patients being dispensed Lotronex are under the care of enrolled physicians. Also, pharmacists will provide Medication Guides to patients whenever Lotronex prescriptions are filled or refilled. The goal is to provide patients with written information about the safe and effective use of Lotronex.
   a. Are the sponsor's proposals to meet each of these goals adequate? If not, describe adequate mechanisms.
   b. Should pharmacist adherence to the program be audited? If so, how?

7. Regarding **safety outcomes**:
   a. Should clinical outcomes (e.g., ischemic colitis, severe constipation, and death) be used to assess the success of the risk-management program? For example, should the rates and/or degree of severity of ischemic colitis and constipation be monitored with the specific goal of evaluating the effectiveness of the program?
   b. If so, specify the adverse events that should be assessed and when the assessment(s) should be made. Describe acceptable rates for these adverse events and/or acceptable degrees of severity.

8. Please provide any additional comments that you may have about a Lotronex risk-management program (e.g., suggestions for additional studies).