Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Gastrointestinal Drugs Advisory Committee

June 27, 2000

Marriott Washington Center
9751 Washington Blvd.
Gaithersburg, MD

Members Present
Stephen Hanauer, M.D., Chair
Loren Laine, M.D.
George D. Ferry, M.D.
Christina M. Surawicz, M.D.
Michael M. Wolfe, M.D.

Consumer Representative
Richard J. Hammes, R.Ph

Consultants to the GIDAC
Richard Blum , M.D.

Guest Experts to the GIDAC
Barry Kramer, M.D.
Amir Kende, M.D.
Jerry Gurwitz, M.D.
Jerry Avorn, M.D.
Joanne Siegel, M.D.

FDA Participants
Florence Houn, M.D.
Victor Raczkowski, M.D.
Lilia Talarico, M.D.
Hugo Gallo-Torres, M.D., Ph.D.
Evelyn Rodriguez, M.D., M.P.H.
Nancy Ostrove, Ph.D.

Sheila Weiss, M.D.

Arthur Levin, M.P.H.
Mark Welton, M.D.
Richard Havlik, M.D.
Neil Powe, M.D.
Eric Holmboe, M.D.

These summary minutes for the June 27 meeting of the Gastrointestinal Drugs Advisory Committee were approved on November 9, 2000.

I certify that I attended the June 27 meeting of the Gastrointestinal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Thomas H. Perez, M.P.H., R.Ph.
Executive Secretary

Stephen Hanauer, M.D.
Chair

On June 27, 2000 the committee discussed risk management of post-marketing adverse events associated with (NDA) 21-107, Lotronex™ (alosetron), Glaxo Wellcome.

The Committee had received a briefing document from Glaxo Wellcome, and the FDA.

There were approximately 150 persons in the audience. The meeting was called to order at 8:30am by the Chair, Stephen Hanauer, M.D. Thomas H. Perez, Executive Secretary of the Gastrointestinal Drugs Advisory Committee read the Meeting Statement. The Committee members and discussants introduced themselves.

Glaxo Wellcome began its presentation at 8:45 am and proceeded as follows.

Introduction	Richard Kent, M.D.
IBS Burden of Illness	Ian M. Gralnek, M.D., M.S.H.S.
Lotronex Safety & Efficacy	Allen Mangel, M.D., Ph.D.
Risk Management Program	Elizabeth Andrews, Ph.D., M.P.H. J. S. Hull
Conclusion	Richard Kent, M.D.

At approximately 11:30 the FDA, CDER presentation was made by

Victor Raczkowski, M.D., Deputy Director, Office of Drug Evaluation III	"Benefit-risk Reevaluation of Marketed Drugs"
Hugo Gallo-Torres, M.D., Ph.D. Medical Team Leader	"Brief Review of Case Reports"
Nancy Ostrove, Ph.D., Branch Chief, Division of Drug Marketing, Advertising & Communications	"Medication Guides"
Evelyn Rodriguez, M.D., M.P.H. Director, Division of Drug Risk Assessment II	"How to Evaluate an Intervention"

The Open Public Hearing portion of the meeting included the following participants:
Nancy Norton, Director, International Foundation for Functional Gastrointestinal Disorders
Richard Krause, M.D., and patients; Sandra Cook, Sandy Conner

The Committee discussed the following questions:

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[7]**

   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?
      Answer: Yes, broadly to physicians, pharmacists and patients.

      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?
      Answer: exclude from therapy individuals with recent constipation.

      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?)
      Answer: Need a rigorous risk factor study to identify patients at risk for non-occlusive disease, use of oral contraceptives and hormone replacement therapy, possible precipitating factors and cofactors of age, etc., probability of risk factors in individuals exhibiting complications.

      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?
      Answer: Need to improve the specificity of diagnosis. Referring patients would create "an accessibility to care issue". Educate, educate, educate.

      v. maintaining the incidence of these toxicities at, or below, a certain level? If so, what are acceptable levels?
      Answer: Risk benefit considerations of therapy should be provided to all patients.

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

Answer: Would want to see a lower risk in the future.

c. Discuss specific criteria (e.g., outcome measures, endpoints) that should be measured to characterize the success of a risk management program for Lotronex.
Answer: Rates should go down regardless of the group receiving the drug. Reassess patients with temporary cessation of therapy, drug holidays, and maintenance trials. Deaths as a result of complications should be examined in context.

d. Discuss when in the risk management program for Lotronex these specific outcome measures should be assessed.
Answer: At the end of 2000.

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[7]'s benefits and risks, and on how to recognize these risks when prescribed the drug), special epidemiological studies or clinical trials (please discuss controls, patient inclusion criteria, endpoints), and limiting distribution of Lotronex[7] to certain patients or physicians.
Answer: Labeling. Also educate patients, physicians, and pharmacist with all means available.

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).
Answer: Use of "Safety and Effectiveness has not been established in" statements. Special education that is appropriate in language and oriented to patients that involves the pertinent foundations. Do communications research to ensure an appropriate level of language. Also education directed to physicians and pharmacists. Use of the web and technology to focus attention on what is important to educate patient seeking treatment and the various health professionals. Use of patient case scenarios to illustrate usage. Use of Medication Guide and Packaging System are recommended. Assess benefit through pharmacy audits. Demand and expect from sponsor a program that works.

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[7] are having their desired impact.
Answer: Utilize surveys to determine what physicians know and evaluate the performance of campaigns undertaken.

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).
Answer: Use of Consent Form. Tie measures to established goals/benchmarks. Evaluate complications occurring and how medication is being prescribed, and the benefits to therapy.

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).
Answer: Evaluate and reassess based on interventions that are taken.

The meeting was adjourned at 3:30 p.m.