Minutes- June 21, 2002

Joint Meeting of the Nonprescription Drugs Advisory Committee with the Gastrointestinal Drugs Advisory Committee

Food and Drug Administration
Center for Drug Evaluation and Research
Holiday Inn, Bethesda

Prilosec (20mgm for 14 days) for OTC use
NDA 21-229, omeprazole magnesium, Astra Xeneca LP/Procter and Gamble

Prior to the meeting, the committee had reviewed background material from Procter and Gamble and from the FDA. The meeting was called to order by Louis Cantilena, M.D., Ph.D. and Sandra Titus, Ph.D, read the conflict of interest statement into the record. There were approximately 225 people in attendance.

Attendance:
NDAC Members Present: Louis Cantilena, M.D., Ph.D., NDAC Chair and Chair of the meeting, Julie Johnson, Pharm.D., Francis Lam, Pharm.D., Donald Uden, Pharm.D., Henry Williams, M.D., Leslie Clapp, M.D., Frank Davidoff, M.D., Sonia Patten, Ph.D.

NDAC Member Recused Self: Alastair Wood, M.D.

NDAC Voting Consultant: Eric Brass, M.D., Ph.D., Edwin Gilliam, Ph.D., Richard Neill, M.D.

GIAC Members Present: Michael Camilleri, M.D., Bryon Cryer, M.D., Ronald Fogel, M.D., Nancy Geller, Ph.D., John Thomas LaMont, M.D., Robert Levine, M.D., Susan Cohen

GI Members Absent: Joel Richter, M.D., Maria Sjogren, M.D.

GIAC Members Recused: Michael Wolfe, M.D., David Metz, M.D.

Industry Guests: (non voting) Michael Alfano, M.D., David Metz, M.D.

FDA Participants:, Jonca Bull, M.D, Charles Ganley, M.D., Linda Katz, M.D., Florence Houn, M.D., Victor Raczkowski, M.D., Hugo Gallo Torres, M.D., Mark Avigan, M.D., Daiva Shetty, M.D., Karen Lechter, J.D., Ph.D.

FDA: Overview Of Today's Issues
Victor Raczkowski, M.D., outlined the purpose of the meeting.

Open Public Hearing Participants:

Linda Golodner, President, National Consumers League, Washington

Robert M. Niecestro, Ph.D. Senior Executive Director, Clinical Research, Adrix Labs, NJ

Susan Winckler, Pharm.D., American Pharmaceutical Association, Washington

Michael Wolfe, M.D., Boston Medical Center, Section of Gastroenterology

Procter and Gamble Presentations:

Overview
Keith C. Triebwasser, Ph.D., Senior Director, Regulatory Affairs, Procter and Gamble

Clinical Perspective
David Peura, M.D., Associate Chief of Gastroenterology, University of Virginia

Efficacy and Consumer Use
Douglas Ws. Bierer, Ph.D., Director OTC Drug Development, Procter and Gamble

Safety Update in the OTC Setting
Douglas Levine, M.D., Chief Medical Officer, Gastrointestinal Therapeutic Area, AstraZeneca

Benefit/Risk
Nora Zorich, M.D., Ph.D., Vice President Pharmaceuticals, Procter & Gamble

Summary
Keith C. Triebwasser, Ph.D.,

FDA Presentations:

Summary of 2000 NDAC/GIAC meeting on Prilosec and Overview of Efficacy
Mark Avigan, M.D., Medical Officer, Division of Gastrointestinal and Coagulation Drug Products

Label Comprehension Studies
Karen Lechter, J.D., Ph.D., Office of Drug Safety

Actual Use Study
Daiva Shetty, M.D., Medical Officer, Division of Over the Counter Drugs

Charge to Committee
Linda Katz, M.D., MPH, Deputy, Division of Over the Counter Drugs
Questions for Committee Deliberation:

Background

Currently, there are two classes of drugs, antacids and acid reducers (histamine-2 receptor antagonists), available in the over-the-counter (OTC) market to treat heartburn. Both, antacids and acid reducers, are indicated for the treatment of acute heartburn symptoms. The acid reducers have an additional claim for the prevention of meal induced heartburn symptoms if ingested at specified times prior to a meal. Omeprazole, a proton-pump inhibitor, is currently indicated for prescription use for the treatment of duodenal and gastric ulcer, symptomatic GERD, erosive esophagitis, and pathological hypersecretory conditions. Clinical efficacy studies with omeprazole have established that it is not effective in treating acute symptomatic heartburn and does not prevent episodic meal induced heartburn (when taken shortly before a meal). Studies have established that omeprazole is most effective in preventing heartburn when taken repetitively on a daily basis. The sponsor is seeking to market Prilosec 1 OTC for the 24-hour prevention of heartburn in the population of frequent heartburn sufferers (defined as suffering heartburn on two or more days per week). The sponsor has proposed a 14-day daily treatment course.

Frequent heartburn may also be the presentation for consumers with serious underlying conditions (e.g. GERD +/- erosive esophagitis). The current direct-to-consumer marketing for prescription Prilosec is directed toward consumers with heartburn symptoms occurring as frequently as two or more days a week and encourages them to contact their physician. For Prilosec 1, the Drug Facts label states that it should be used for frequent heartburn and only for those who suffer heartburn two or more days per week. Thus, the same symptomatic heartburn population will be directed to either use Prilosec 1 or prescription Prilosec.

1. **Population**
   If Prilosec is available OTC, the sponsor acknowledges that some consumers with GERD +/- erosive esophagitis will choose to use Prilosec 1**. Is it acceptable that some patients with GERD +/- erosive esophagitis self-treat with OTC medication?** Please explain under what circumstances this is acceptable or not acceptable.

   Yes= 16 No= 22.

2. **Has the sponsor demonstrated that consumers with heartburn can adequately self-select use of Prilosec 1?** When answering this question consider the data provided in the labeling comprehension studies and actual use study for use by individuals:
   - having < 2 heartburn episodes per week;
   - with relative contraindications for use that require a discussion with a physician before use;
   - desiring acute symptomatic relief; and
   - episodically (not on a daily basis).

   Yes= 3 No= 15

   Most committee members felt that the actual use study did not demonstrate adequate self selection and that the label used for the actual use studies was inadequate.

3. **Actual Use**

In the actual use study, the sponsor provides information on the behavior of consumers who have a reoccurrence of heartburn symptoms after completing the 14-day course of therapy. **Did consumers who had a reoccurrence of heartburn symptoms respond appropriately?** When answering this question comment on the likelihood that consumers will seek advice from a health care professional (HCP) or the likelihood of the consumer using the product again without the advice of a HCP. Describe any other data in the submission that support your answer.

Yes= 12 No= 6

Many on the committee felt that while people did not follow the instructions in the study as desired, that what the majority did was reasonable and that they would be likely to do another course of therapy. Also, while it might be nice if people would go to see their doctor if the treatment failed, we can't expect that they will go to see a physician because their symptoms return.

Those who voted no on this question felt that only 20 % went to their provider; the study was too short to determine if people would go and take more Prilosec or go and see a physician. There was concern that when consumers were not responsive to therapy that we should want them to see a physician to rule out something more serious.

3. **Duration and Repeat Use**

- **Given that the treatment for GERD with erosive esophagitis is a minimum of 28 days, is the proposed 14-day duration of therapy acceptable for this population?**

Yes= 17 No= 1

Fourteen days was viewed as acceptable for several different reasons. It was better to have an effective drug that might work in the majority of symptomatic consumers. One GI member pointed out that even if treated for 28 days that some would have a re-occurrence but, that it will just take longer for that to happen if a consumer took it for two 14 day cycles. Another GI member pointed out that 14 days is a balance between efficacy and masking of worrisome symptoms.

4. **Approvability**

Has the sponsor provided sufficient information to support the approval of Prilosec 1 for the prevention of frequent heartburn? Please describe the data that influenced your decision.

Yes= 16 No= 2

If the committee recommends approval:

- Should the labeling specify a time period after which another course of Prilosec 1 can be taken without the need to speak to a physician (e.g. the consumer develops frequent heartburn 6 months after the initial course of Prilosec 1)?
- ***Some members felt that a repeat every three or four months would be appropriate.***

- If yes, is there a limit on the number of courses a consumer should take over a period of time?

  Many members thought that two to three times in a year would be a reasonable repeat pattern.

- Are their any additional labeling or marketing suggestions that might assure the appropriate use of Prilosec 1 (e.g. should the label state what types of heartburn Prilosec is not effective in treating)? Given that Prilosec 1 and prescription Prilosec will be marketed to the same symptomatic population, please explain how a consumer should determine the appropriate course of action when they experience frequent heartburn (i.e. purchase the OTC product or contact a physician).

  No committee member felt that the label submitted by the sponsor was adequate for OTC marketing of this product.

  There were many labeling recommendations:

  Need for clear warning about heart/chest problems

  Drug interactions – enhance warnings, possibly using the trade name instead of chemical name

  "DON'T USE"is better than "ASK YOUR DOCTOR"

  Label that 2-3 course / year acceptable (This was the maximum number of 14 day cycles that the committee felt was acceptable.)

  Use of the word prevention is confusing

  Don't use acid reducer – not clear

  Warning not to use H2blockers with this medication

  Why not warn consumers not to use Prilosec if using an antifungal agent ?

  Explain how this is different from other heart burn medications

What can be used for symptom relief while waiting for Prilosec to kick in?

Overview
Eleven of the members felt that a new label /actual use study should be done before approval. One member voted no. (At least four seats were vacant at the time of the vote.) Specifically, the committee emphasized that consumers' ability to adhere to limiting the number of cycles as well as following other labeling changes should be determined by label comprehension studies/measures of usage patterns before approval. Several members recommended adequate testing of an improved label, especially in the low literacy subpopulation of potential consumers (a group that did poorly in the label comprehension studies submitted by the sponsor).

- Should the agency require any phase IV commitments to assess the appropriate use of Prilosec 1?

The committee recommended pre-approval studies rather than phase IV.

If the committee does not recommend approval:

- What additional information needs to be provided by the sponsor to support the approval of Prilosec 1?

Label the product as having a drug interaction with digoxin

A verbatim transcript of this meeting will be available on the FDA's Dockets Management Branch Website approximately 30 days after the meeting. The address is HTTP://www.fda.gov/ohrms/dockets/ac/acmenu.htm.

I certify that I attended the June 21, 2002 meeting of the Joint Meeting of the Nonprescription Drugs Advisory Committee with the Gastrointestinal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/S/ _____ **/S/**

Sandra Titus, Ph.D. Date
Executive Secretary, NDAC

Louis Cantilena, M.D., Ph.D. Date
Chair, NDAC

Prepared by Titus, June 21, 2002