Final Minutes

October 20, 2000 - Joint Meeting of the
Nonprescription Drugs & Gastrointestinal Advisory Committees
Food and Drug Administration
Center for Drug Evaluation and Research
Holiday Inn, 2 Montgomery Avenue, Gaithersburg, MD
Prilosec 1™
(omeprazole magnesium, Astra Zeneca & Procter & Gamble, NDA 21-229)

The meeting was held at the Holiday Inn, Gaithersburg, MD. Prior to the meeting, the members, consultants and guests had reviewed background material from the FDA and from the sponsor. In order for the public to be informed, the background material was also available on the Dockets page the day before the meeting. There were approximately 200 persons in attendance. The meeting started at 8 a.m. and ended at 5:00 p.m.

Attendance:
NDAC Members Present: Eric Brass, M.D., Ph.D., Chair, Richard Neill, M.D., Edwin Gilliam, Ph.D., Julie Johnson, Pharm.D., Hari Sachs, M.D., Louis Cantilena, M.D., Ph.D., Francis Lam, Pharm.D., Donald Uden, Pharm.D., George Blewitt, M.D.(non-voting)

NDAC Members Absent: Edward Krenzelok, Henry Williams, M.D

GIAC Members Present: William Steinberg, M.D., Nancy Geller, M.D.,

GIAC Members Absent: Christina Surawicz, M.D., George Ferry, M.D., Joanne A. P. Wilson, M.D., Joel Richter, M.D., Michael Wolfe, M.D., Maria Sjogren, M.D.

SGE Consultants: Statisticians: Ralph D'Agositino, Ph.D., Janet Elashoff, Ph.D., Samuel Shapiro, M.B.B.Ch.; **Consumer Representative:** Susan Cohen

Non-voting Guest – Sidney Cohen, M.D., George Sachs, M.D., Helge Waldum, M.D., Malcolm Robinson, M.D., George Douglas, Ph.D., Marvin Shuster, M.D., Jon Mirsalis, Ph.D.

FDA Participants: Robert DeLap, M.D., Ph.D., Victor Raczkowski, M.D., Charles Ganley, M.D., Linda Katz, M.D., MPH, Larry Goldkind, M.D., Ling Chin, M.D., MPH, Mark Avigan, M.D., Karen Lechter, J.D., Ph.D.

Astra Zeneca and Procter & Gamble Presentations
Douglas Ws. Bierer, Ph.D., Director, Regulatory Affairs introduced the issues. Donald O. Castell, M.D gave an overview of the role of proton pump inhibitors in the self-management of heartburn. Nora Zorich, M.D., Ph.D., described the Omeprazole-Mg OTC efficacy trials. Bernard P. Schachtel, M.D., reviewed the consumer usage patterns in OTC settings. Doug Levine, M.D., described the safety profile of omeprazole.

FDA Presentations:
Charles Ganley, M.D. gave an overview of the issues to be explored by the committee. Larry Goldkind, M.D., reviewed the efficacy data. Ling Chin, M.D., MPH, described the Actual Use Trials. Mark Avigan, M.D., presented safety issues. Karen Lechter, J.D., Ph.D. reviewed the Label Comprehension data. Linda Katz, M.D., MPH gave the charge to the committee.

Open Public Hearing
There were no presenters.

Committee Discussion and Vote:
Currently, there are two classes of drugs, antacids and acid reducers (histamine-2 receptor antagonists), available in the OTC market to treat heartburn. Both antacids and acid reducers are indicated for the treatment of acute occasional 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. At today's meeting, the sponsor is seeking the approval of omeprazole in the OTC setting for these indications and for the additional indication of 24-hour prevention of heartburn. Omeprazole, a proton-pump inhibitor, is currently indicated Rx for the treatment of duodenal and gastric ulcer, symptomatic Gastroesophageal Reflux Disease (GERD), erosive esophagitis, and pathological hypersecretory conditions. In support of the proposed OTC marketing, the sponsor conducted studies to evaluate the efficacy of omeprazole 10 mg and 20 mg for the treatment of acute symptomatic heartburn (studies 092, 095, 017, 018, 019), for the prevention of meal induced heartburn (studies 005 and 006) and for the 24 hour prevention of heartburn (studies 171 and 183). They also conducted five actual use studies (studies 003, 067, 014, 022 and 091) to evaluate consumer usage patterns and dosing compliance.

The committee discussed the questions as well as voted on them. You are referred to the transcript for the discussion of the questions.

A. In **studies 092 and 095**, the primary endpoint for efficacy was the occurrence of **sustained complete relief of the first treated episode of heartburn**. Based on the primary measure of efficacy, is there a clinically significant improvement of acute symptomatic heartburn in either the 10 or 20-mg omeprazole groups compared to placebo? Please explain your answer.

No= 13 Yes=0 Abstain=1

B. In studies **005 and 006**, the primary endpoint for efficacy was the percentage of subjects heartburn-free over the entire **four-hour period after a provocative meal.**

1. Based on the primary measure of efficacy, is there a clinically significant improvement of heartburn symptoms in either the 10 or 20 mg omeprazole groups compared to placebo? Please explain your answer.

No= 13 Yes=1 Abstain=0

2. Are the analyses of the pre-specified secondary endpoints supportive of the primary study outcome? Do they add information regarding clinically significant treatment effect?

   There was consensus that there is some consistency in favor of drug for the secondary endpoints.

C. In studies **171 and 183**, the primary endpoint for efficacy was the complete **prevention** of heartburn between the first two doses of therapy.

1. Based on the primary measure of efficacy, is there a clinically significant improvement of heartburn symptoms in either the 10 or 20 mg omeprazole groups compared to placebo? Please explain your answer.

No= 0 Yes= 14 Abstain=0

2. Are the analyses of the pre-specified secondary endpoints supportive of the primary study outcome? Do they add information regarding clinically significant treatment effect?

   There was consensus that there is some consistency in favor of drug for the secondary endpoints.

D. Based on the types and frequency of adverse events reported in the clinical trials and in the post-marketing adverse events database, are the safety concerns for the OTC marketing of omeprazole able to be addressed solely by labeling (identifying risks) to consumers for (a) short term or (b) chronic intermittent use? In answering this question, please consider the reports of anaphylaxis/angioedema/urticaria, liver toxicity, white blood cell disorders and severe skin reactions.

Can Not Do in Label = 7	**Can Do in Label =5**	**Abstain =2**

E. Do other safety concerns affect acceptability of the OTC marketing of omeprazole? In answering this question, please consider the questions raised by the FDA reviewer regarding: 1) the masking of serious disease; 2) the potential for genotoxicity, tumorigenicity, and fetal and developmental toxicity; 3) rebound hyperacidity reported in the literature with discontinuation of therapy; and 4) hypergastrinemia that may be associated with the chronic or chronic intermittent use of omeprazole.

There was confusion over what yes and no meant and so there was a re-vote. The following only records the re-vote:

8 = No (safety can be addressed appropriately for use)
5 = Yes (safety can not be addressed appropriately for use)
1= Abstain

F. Are there drug-drug interactions that affect acceptablity of OTC marketing of omeprazole?

No vote taken. There was discussion at different times about what is and is not known about drug-drug interactions.

G. In the actual use studies, approximately 65% of the subset of subjects using the product only for the prevention of heartburn exceeded the 10 consecutive day limit for dosing recommended on the label. (Note: 19% to 22% of consumers using omeprazole for both acute symptoms and prevention similarly exceeded the 10 consecutive day limit for dosing recommended on the label). Do these results suggest that omeprazole will likely be used by consumers on a chronic basis for conditions other than episodic heartburn (e.g. GERD)? Is the treatment of GERD an acceptable OTC indication?

The Chair altered the question by adding the clause on chronic heartburn to the question. Thus the question now:

Is the treatment **of chronic heartburn** or GERD an acceptable OTC indication?

7= Yes acceptable for OTC
6 = Not acceptable OTC
1=abstain

H. Based on the results of the actual use and label comprehension studies, has the sponsor presented adequate data to substantiate that consumers will be able to use omeprazole appropriately in the OTC setting for: 1) acute symptomatic treatment; 2) prevention for up to 10 days.

No Vote

In responding, consider these factors:

a) The ability of consumers to appropriately self-select.
b) The ability of consumers to use the correct dosage and for the period of time specified in the label.
c) The ability of consumers to identify when they should see a physician before using the product and once they have begun using the product.
d) The ability of consumers to identify serious adverse events.
e) The ability of consumers to avoid interacting drugs.
f) Use in women of childbearing age or in the pediatric population.

Risk to benefit question:

I. Has the sponsor provided sufficient evidence to support the approval of omeprazole 10 mg and/or 20 mg for use in the OTC setting for:

1. Acute symptomatic heartburn? Please explain.
2. Prevention of episodic or chronic heartburn? Please explain.

a) If yes to either, are there any additional studies or risk management programs needed post-approval?

b) If no, what additional studies or risk management programs are necessary to support approval for OTC marketing?

The Chair altered the question into the following subquestions

Has the sponsor provided sufficient evidence to support approval:

(NO means that there is no evidence of demonstration of efficacy/safety. Inversely, Yes means that risk benefit ratio is acceptable for the OTC setting to support approval.

10 mg for indication of acute symptomatic heartburn

No= 11 YES= 2 Abstain=0

20 mg for indication of acute symptomatic heartburn

No= 11 YES= 2 Abstain=0

10 mg for indication to prevent episodic heartburn

No= 10 YES= 2 Abstain=1

20 mg for indication to prevent episodic heartburn

No= 10 YES= 2 Abstain=1

10 mg for indication of chronic heartburn

No= 9 YES= 3 Abstain=1

20 mg for indication of chronic heartburn

No= 9 YES= 3 Abstain=1

J. If the Committee recommends approval of omeprazole for use in the OTC setting, please discuss any recommendations regarding information to be conveyed in labeling (e.g., to help consumers select between omeprazole and other currently available OTC products, and to help consumers use omeprazole safely and effectively).

Issue discussed in context of other questions.

Each of the above questions had lengthy discussions where members elaborated on why they voted as they did. You are referred to the transcript for this narrative account.

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 October 20, 2000 meeting of the Nonprescription Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Sandra Titus 11-1-00

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

11/13/00

Eric Brass, M.D., Ph.D. Date
Chair, NDAC