CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020406/S016

Trade Name: PREVACID DELAYED-RELEASE CAPSULES

Generic Name: LANSOPRAZOLE

Sponsor: TAP HOLDINGS, INC.

Approval Date: 03/12/98

Indication(s): SHORT TERM TREATMENT OF SYMPTOMATIC GASTROESOPHAGEAL REFLUX DISEASE (GERD)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020406/S016

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	Included	Pending Completion	Not Prepared	Not Required
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Final Printed Labeling				X
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)				X
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020406/S016

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-406/S-016

TAP Holdings Inc.
Attention: Judy Decker Wargel
2355 Waukegan Road
Deerfield, IL 60015

MAR 12 1998

Dear Ms. Wargel:

Please refer to your supplemental new drug application dated December 20, 1996, received December 23, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated October 31, 1997, January 5 and 23, February 20, and March 9, 1998. The User Fee goal date for this application is September 10, 1998.

The supplemental application provides for a new indication: short-term treatment of symptomatic gastroesophageal reflux disease (GERD).

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on March 9, 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

We recommend that the following editorial revisions to the labeling be incorporated at the next printing of the package insert:

1. Under INDICATIONS AND USAGE

   The heading, "**Short-Term Treatment of Erosive Esophagitis,**" should be unbolded and italicized so that it becomes a subheading under the heading of **Gastroesophageal Reflux Disease (GERD)**, along with the subheading, "*Short-Term Treatment of Symptomatic GERD*."

2. Under DOSAGE AND ADMINISTRATION

   The heading, "**Treatment of Erosive Esophagitis,**" should be unbolded and italicized so that it becomes a subheading under the heading, **Gastroesophageal Reflux Disease (GERD)**, along with the subheading, "*Treatment of Erosive Esophagitis.*"

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020406/S016

APPROVABLE LETTER

NDA 20-406/S-016

FEB 18 1998

TAP Holdings Inc.
Attention: Judy Decker Wargel
2355 Waukegan Road
Deerfield, IL 60015

Dear Ms. Wargel:

Please refer to your supplemental new drug application dated December 20, 1996, received December 23, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated October 31, 1997 and January 5 and 23, 1998. The User Fee goal date for this application is March 6, 1998.

The supplemental application provides for a new indication: short-term treatment of symptomatic gastroesophageal reflux disease (GERD).

We have completed the review of this supplemental application as submitted with revised draft labeling, dated January 5, 1998, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as follows.

Under CLINICAL STUDIES:

APPEARS THIS WAY
ON ORIGINAL

1. Delete the following paragraph:

   "The intent-to-treat analyses demonstrated significant reduction in frequency and severity of day and night heartburn. After a single dose, 45% and 39% of patients treated with lansoprazole 15 mg and lansoprazole 30 mg, respectively, reported no day heartburn compared to 19% of patients receiving placebo. Likewise, the percentage of patients reporting no night heartburn were 61%, 51%, and 31%, respectively."

2. Following the sentence, "Data for the 8-week treatment period were as follows:", delete the two graphs and insert Figures 8.1.1.a and 8.1.1.b found in Volume 14 of the original supplement.

Please submit 20 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely yours,

/S/ 2-11-98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:

Original NDA 20-406/S-106
HFD-180/Div. Files
HFD-002/ORM
HFD-103/Office Director
HFD-101/L.Carter
HFD-92/DDM-DIAB
HFD-40/DDMAC (with draft labeling)
DISTRICT OFFICE
HFD-180/PM/M.Walsh
HFD-180/J.Senior

Drafted by: M.Walsh 2/11/98
Initialed by: L.Talarico 2/12/98
Final: M.Walsh 2/17/98
filename: 20406S16.ae2

APPROVABLE (AE)

NDA 20-406/S-016

DEC 22 1997

TAP Holdings Inc.
Attention: Judy Decker Wargel
2355 Waukegan Road
Deerfield, IL 60015

Dear Ms. Wargel:

Please refer to your supplemental new drug application dated December 20, 1996, received December 23, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

We acknowledge receipt of your submission dated October 31, 1997. The User Fee goal date for this application is December 23, 1997.

The supplemental application provides for a new indication: short-term treatment of symptomatic gastroesophageal reflux disease (GERD).

We have completed the review of this supplemental application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

1. Under CLINICAL STUDIES

Gastroesophageal Reflux Disease (GERD)
Symptomatic GERD
In a U.S. multicenter, double-blind, placebo-controlled study of 214 patients with frequent GERD symptoms, but no esophageal erosions by endoscopy, significantly greater relief of heartburn associated with GERD was observed with the administration of lansoprazole 15 mg once daily up to 8 weeks than with placebo. No significant additional benefit from lansoprazole 30 mg once daily was observed.

Please insert the efficacy results (i.e. relief of day and night heartburn) of the intent-to-treat patient population after this paragraph. We suggest either a graph or a table with the following time points: 0, 2, 7, 14, 28, and 56 days.

2. Under INDICATIONS AND USAGE

Gastroesophageal Reflux Disease (GERD)
Short-Term Treatment of Symptomatic GERD
PREVACID Delayed-Release Capsules are indicated for the treatment of

heartburn and other symptoms associated with GERD.

3. Under DOSAGE AND ADMINISTRATION

Gastroesophageal Reflux Disease (GERD)
Treatment of Symptomatic GERD
The recommended adult oral dose is 15 mg once daily for up to 8 weeks.

In addition, all previous revisions as reflected in the most recently approved package insert must be included.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely yours,

/S/ 12-22-97

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020406/S016

MEDICAL REVIEW(S)

DEC 19 1997

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW OF NEW DRUG APPLICATION (NDA) SUPPLEMENT

NDA:	20-406 SE1-016 (supplemental new efficacy indication)
SPONSOR:	TAP Holdings Inc. 2355 Waukegan Road, Deerfield, IL 60015
DATE OF SUBMISSION:	20 December 1996
DATE OF RECEIPT:	23 December 1996
ASSIGNED FOR REVIEW:	15 January 1997
DRUG:	Lansoprazole (PREVACID®) delayed-release capsules
ROUTE OF ADMINISTRATION:	Oral, 30 mg daily, for 4 to 8 weeks
PROPOSED INDICATIONS:	Treatment of non-erosive gastroesophageal reflux symptoms (heartburn, abdominal pain)
MATERIAL REVIEWED:	Supplemental application: proposed labeling; background references (55 volumes); previous reviews; supplement SE1-002 submitted 18 May 1995; pertinent literature.
REVIEWER:	John R. Senior, M.D./ 19 December 1997

Overall Review Summary

Lansoprazole was originally approved on 10 May 1995 for healing of active or acute duodenal ulcers and esophageal erosions, then approved on 8 April 1996 for up to one year maintenance of healing of erosive esophagitis, on 17 April 1997 for up to a year maintenance of healing of duodenal ulcer, and on 8 May 1997 for healing gastric ulcer. It is similar in its pharmacologic and clinical effects to omeprazole, the parent drug in the series of "proton-pump inhibitors" that profoundly suppress gastric acid secretion.

The data show that lansoprazole 15 mg daily for up to 8 weeks is effective in reducing symptoms of heartburn and other symptoms in patients with gastroesophageal reflux but no demonstrable erosive esophagitis. No additional benefit has been demonstrated for use of 30 mg daily. It is recommended that this supplemental indication may be approved at this time, but it is suggested that additional data should be obtained on long-term safety post-marketing, particularly if patients use lansoprazole repeatedly for 8-week periods of symptom relief.

Long term use of these proton pump inhibitors was allowed when it became apparent from extensive clinical experience that humans did not show the increased incidence of various gastric and other tumors that had been seen in rodent models after long-term exposure. However, recent reports have indicated that the long-term administration of omeprazole in humans possibly may accelerate the progression of chronic gastritis associated with Helicobacter pylori infection (Hp) to atrophic gastritis, formerly believed to be a possibly premalignant condition, but long-term data are insufficient to permit firm conclusions on this matter. Further data will be needed to establish whether the infection should be eradicated before starting long-term lansoprazole treatment.

NDA 20-406/SE1-016 Medical Review

Table of Contents

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ON ORIGINAL

Note: In this review, blocks of commentary in italic print are from the reviewer's critique, questions, interpretations, or observations, to distinguish them from data, analyses, or conclusions offered by the sponsor or summarized by the reviewer from their submitted material.

cc:

Original NDA 20-406/S-016
HFD-180/Div. Files
HFD-002/ORM
HFD-103/Office Director
HFD-101/L.Carter
HFD-92/DDM-DIAB
HFD-40/DDMAC (with draft labeling)
DISTRICT OFFICE
HFD-180/CSO/M.Walsh
HFD-180/J.Senior

Drafted by: M.Walsh 12/16/97
Revised: M.Walsh 12/17/97
Initialed by: L.Talarico 12/17/97
Final: M.Walsh 12/18/97
filename: 20406S16.AE

APPROVABLE (AE)

I. Background and Introduction

Lansoprazole (PREVACID®, prev'-a-sid, AG-1749, TAP Holdings Inc.), a substituted benzimidazole derivative, was originally developed in 1982 and was first studied in man in 1985 at the Central Research Laboratories of Takeda Chemicals Industries Ltd. in Osaka, Japan. The first studies of lansoprazole capsules in the United States were begun in May 1987 The NDA was submitted 12 November 1993, and approval was granted 10 May 1995 for use of lansoprazole in daily oral doses of 15 mg once daily for up to 4 weeks for healing of acute duodenal ulcers, 30 mg once daily for up to 8 weeks for healing of erosive reflux esophagitis, and 60 mg daily or more for indefinite time for patients with Zollinger-Ellison syndrome or other pathological hypersecretory conditions.

In May 1995, after approval of lansoprazole for short-term indications in healing of erosive reflux esophagitis and duodenal ulcer, an application for use of lansoprazole for maintenance of healing of erosive esophagitis was resubmitted by TAP Holdings (supplement S-002 to NDA 20-406), supported by additional long-term clinical use data from the second safety update submitted 18 August 1995 as Amendment-001 to S-002, comprising 91 volumes of data. Based on review of that material, lansoprazole at a daily morning dose of 15 mg for up to one year was approved 8 April 1996 for prevention of recurrence of erosive esophagitis after healing. The principal safety concerns that were considered in reaching approval were based on data from rodent species that showed increased incidence of tumors of the stomach and other organs in animals exposed to long-term, often high-dose lansoprazole administration. Similar concerns had delayed the approval of omeprazole for long-term use in the United States for almost 6 years after its approval for healing esophageal erosions. However, very extensive clinical use of omeprazole, and later of lansoprazole, led to a growing sense that the human experience did not reflect the predictions of the rodent toxicologic-tumorigenic models. Accordingly, both omeprazole and lansoprazole have been approved for long-term (up to one year) administration at half-healing doses for maintenance of healing of erosive reflux esophagitis. In addition, lansoprazole was approved in April 1997 for up to a year maintenance of healing of duodenal ulcers, regardless of Hp status, and in May 1997 for healing of gastric ulcer..

This supplemental application, submitted to the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) of the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA), now requests approval of the same dose of lansoprazole, 30 mg once daily before breakfast each morning for 4 to 8 weeks, as that approved for healing of erosive esophagitis, for treatment of the *symptoms*, especially heartburn and abdominal pain, of *non-erosive* gastroesophageal reflux disease (GERD).

This review of SE1-016 to the New Drug Application (NDA) 20-406 is formatted according to the *Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications* (HHS/FDA/CDER July 1988) and the provisions of 21 CFR 314.50: Content and Format of an Application. Reference is also made to the medical review (Dr. H. Gallo-Torres) of NDA 20-406 submission of 23 November 1993, approved 10 May 1995.

A. Drug Substance and Product

The chemical agent and formulation proposed for this supplemental use have already been reviewed and approved for clinical treatment in the healing of duodenal ulcers, healing of erosions from reflux esophagitis and maintenance of healing by prevention of recurrence. There is no need to review in depth further in this document the proposed formulation of (PREVACID®) delayed-release capsules.

B. Summary of Pre-Clinical Pharmacology

No new animal or clinical data on toxicology, pharmacokinetics, or pharmacodynamics were submitted with this application for the supplemental use of lansoprazole for long-term maintenance treatment to prevent recurrence of duodenal ulcer after healing. The data on pharmacology and toxicology were reviewed extensively at the time of the original NDA 20-406 submission of 23 November 1993 (see review by Gallo-Torres, 1994; and review by pharmacologist, J. Chopra, 1993).

C. Summary of Human Pharmacokinetics, Metabolism

The data on pharmacokinetics and metabolism in man were reviewed extensively at the time of the original NDA 20-406 submission of 23 November 1993 (see review by Gallo-Torres, 1994). In brief, the oral formulation of two 15 mg tablets used in the studies of duodenal ulcer healing and recurrence showed Cmax of about 800 ng/mL at about 1.6 hours (Tmax) after oral administration, an area under the AUC from administration to undetectability was about 1900 ng-h/mL, and the half-time ($T_{½}$) of disappearance was about 1.4 hours, although there was substantial individual patient variation from these mean-median values, with coefficients of variation of about 50% for Cmax and Tmax, 66% for $T_{½}$, and 84% for AUC. Lansoprazole was well absorbed, with an absolute bioavailability of 0.86 for the 15 mg dose and 0.80 for a 30 mg dose, indicating a relatively low first-pass (hepatic) effect, but some decrease if given after food. When administered concurrently or within an hour after an antacid (Maalox, Riopan), the Cmax was reduced significantly but the AUC was not significantly changed. Daily dosing at 8 a.m. in the morning (mane) showed better bioavailability than evening dosing at 10 p.m. (nocte).

The metabolism of lansoprazole in man occurs by pathways similar to those in rats and dogs, with rapid breakdown extensive binding of the drug and its metabolites to plasma proteins

and better absorption from the gastrointestinal tract (about 80%) than in rats or mice (4%) of dogs (22%). Large intersubject variability in absorption was observed, but in given individuals the amounts absorbed were roughly proportional to dose ingested. Multiple dosing over periods of time did not lead to accumulation, and plasma drug levels were zero (undetectable) before the next dose on a schedule of once-daily dosing. Older patients or subjects showed greater AUC and $T_{½}$ values, but similar Cmax and Tmax values, indicating slower clearance, but still no accumulation before the next daily dose. Effects in people with impaired renal or hepatic function also showed delayed clearance but no change in uptake, and no accumulation on daily dosing. Lansoprazole did not show

any important clinical interactions with some other drugs, including warfarin, indomethacin, ibuprofen, aspirin, phenytoin, prednisone or diazepam, but the reviewer (Gallo-Torres) emphasized that drug-drug interaction studies were incomplete. No new data were supplied with this supplement.

D. Summary of Human Pharmacodynamics

When the pharmacodynamic effects of once-daily dosing of lansoprazole 15 or 30 mg were compared with omeprazole 20 mg, the results showed great overlap in serial mean gastric pH values over the 24-hour period, all very significantly greater than placebo but not from each other. Very few data were obtained for lower lansoprazole doses of 7.5 or 10 mg. There was no evidence that using split doses b.i.d. was more effective in gastric acid suppression that once-daily dosing. There seemed to be a trend toward slightly better acid suppression at daily doses of 30 mg than at 15 mg, but no advantage of 60 mg over 30 mg. It was not clear how those dose-ranging studies would inform the choice of an optimum dose for clinical healing of esophagogastroduodenal lesions.

E. Summary of Previous Clinical Trials and Approved Uses

The original NDA 20-406 submitted 23 November 1993 was reviewed (Gallo-Torres, 1994; Chopra, 1994) and discussed at the December 1994 meeting of the Gastrointestinal Advisory Committee (transcript, 1995). These actions and interpretations led to recommendation for approval of lansoprazole for healing of duodenal ulcers (15 mg once daily for up to 4 weeks) and also for healing of erosive esophagitis (30 mg once daily for up to 8 weeks) and treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome (60 mg once daily, or higher doses as needed, long-term, without specified duration limit).

Based on review of additional clinical data, lansoprazole at a daily morning dose of 15 mg for up to one year was approved 8 April 1996 for prevention of recurrence of erosive esophagitis after healing. The principal safety concerns that were considered in reaching approval were centered on data from rodent species that showed increased incidence of tumors of the stomach and other organs in animals exposed to long-term, often high-dose lansoprazole administration. Similar concerns had delayed the approval of omeprazole for long-term use in the United States for almost 6 years after its approval for healing esophageal erosions. However, very extensive clinical use of omeprazole, and later of lansoprazole, led to a growing sense that the human experience did not reflect the predictions of the rodent toxicologic-tumorigenic models. Accordingly, both omeprazole and lansoprazole have been approved for long-term (up to one year) administration at half-healing doses for maintenance of healing of erosive reflux esophagitis. In addition, lansoprazole was approved in April 1997 for up to a year maintenance of healing of duodenal ulcers, regardless of whether or not patients were infected with Helicobacter pylori (Hp), and in May 1997 for healing of acute gastric ulcer..

II. Reports of Studies for Treatment of Symptoms of GERD

A. Investigators

Results of two principal studies have been submitted in support of this application for a new indication for clinical use of lansoprazole for **short-term treatment (4 to 8 weeks) for relief of symptoms including heartburn and abdominal pain (in patients with non-erosive esophagitis) associated with gastroesophageal reflux disease** (GERD). The two principal studies are: 1) a re-analysis of a subset of 106 patients without endoscopically demonstrated esophageal erosions from the whole set 292 patients entered into Study **M87-092**, aimed primarily at demonstrating healing of erosive esophagitis; and 2) a new Study **M95-300**, in 214 patients with frequent symptoms of GERD but no erosions by initial endoscopy. Results have also been provided of re-analysis of another study, **D75p501**, involving a comparison with effects of ranitidine, that was carried out in the United Kingdom with another 57 patients that again represented a subset without erosions from a total of 229 patients enrolled.

Comment: More exactly, the claim appears, from the data obtained, to mean reduction in the ... idence or occurrence of the symptoms during future periods of treatment, compared to that experienced in similar periods of time before treatment. It does not appear to mean immediate relief of symptoms already present at the moment medication is taken.

Names and locations of the investigators are listed below in sections on the individual reports. There were 27 of the 34 investigators in M87-092 who had at least one patient with endoscopic evidence of no erosions, plus another 18 investigators in M95-300, who participated in these studies in the United States, and 4 of 5 in the U.K. who participated and had at least one patient without erosions.

B. Background and Overview of Clinical Investigations

The principal clinical evidence to support use of lansoprazole for symptomatic treatment of GERD, is based on the two trials mentioned above, Studies M87-092 and M95-300. In addition, another supportive study was carried out in England and the results submitted with this application. Two of these three studies represent *post hoc* re-analyses of studies done many years ago for the purpose of demonstrating the effectiveness of lansoprazole in healing erosive esophagitis. When candidates for those studies, M87-092 and D75p501, were found at endoscopy not to have erosions but only mucosal friability (then classified as Grade 2 esophagitis using the system of Kaul, et al., 1986, they were entered and randomized anyway, and data on symptomatic responses were gathered. In this submission, the subset re-analyses of data from 106/292 U.S. patients from Study M87-092 and 57/229 U.K. patients from D75p301 are submitted. The full study reports from both studies were submitted with the original NDA 20-406 on 12 November 1993. The more recent study, M95-300, was carried out in 1995-6 to add additional evidence. In this submission, Study M87-092 is dealt with in Volumes 4 to 13, Study M95-300 in Volumes 14 to 18, and Study D75p501 in Volumes 19 to 22. Overall summaries are presented in Volumes 1-3 and 23-26.

PLACEBO-CONTROLLED, RANDOMIZED STUDIES OF NON-EROSIVE ESOPHAGITIS

Trial	*Study Design*	*Treatment Arms*				*Effectiveness Outcome*
		L15	*L30*	*L60*	*Pla*	
M87-092 1988-9	Placebo-controlled, fixed dose, randomized, double blind, parallel-group, 8-week, multicentered study.	23	24	32	27	Day and night abdominal pain was significantly less on lansoprazole 30 and 60 mg/day, in severity and percent of days experienced; significantly fewer Gelusil tablets were required for relief.
M95-300 1995-6	Placebo-controlled, fixed dose, randomized, double blind, parallel-group, 8-week, multicentered study.	82	88	0	44	Day and night heartburn was significantly less severe with both lansoprazole doses, during the first 4 weeks and over the whole 8 weeks; significantly fewer Gelusil tablets were needed for relief.

**Note: L15, L30, L60 mean lansoprazole 15, 30, 60 mg/day; Pla, placebo.*

SUPPORTIVE EUROPEAN STUDIES OF DUODENAL ULCER RECURRENCE

Trial	*Study Design*	*Treatment Arms*			*Effectiveness Outcome*
		L30	*L60*	*R300*	
Active agent-controlled studies					
D75p501 UK 1988-90	Randomized, double-blind, ranitidine-150 controlled, fixed-dose, multicentered	19	20	18	Once daily lansoprazole 30 or 60 mg heals lesions of esophagitis and reduces symptoms significantly better than ranitidine 150 bid; no significant difference between the lansoprazole doses was observed.

**Note:, L30, L60 mean lansoprazole 30 or 60 mg once/day; R300, ranitidine 150 mg twice/day.*

Comment: The above three studies comprise the clinical data support for the sponsor's claim for approval of lansoprazole 30 mg daily before breakfast for 4 to 8 weeks for relief of heartburn and abdominal pain associated with GERD in patients with non-erosive esophagitis.

Although the two U.S. studies are listed by the sponsor as principal or "pivotal" studies for this indication, and the U.K. study as supportive, it may be argued that the retrospective re-analysis of M87-092 for a subset of 106 out of the whole 292 patients enrolled is really a "fishing expedition" in which significant findings in that subset were searched for by a great multiplicity of statistical analyses of many variables other than those retrospectively claimed to be important, namely abdominal pain. The detailed discussions and commentary below, where individual studies are evaluated in some depth, may bring out these points more clearly.

Neither M87-092 or D75p501 was designed to show relief of symptoms as the primary outcome measure, and the main population studies was patients with erosive esophagitis. The emphasis at that time was on seeking approval for healing of the erosions/ulcerations, not symptom relief.

C. Choice of Dose for Symptomatic Treatment of Non-Erosive GERD

The sponsor presents in the opening volume of this submission an overview of the three clinical trials done and summarized for this submission. From them the sponsor concludes very tersely (page 270, Volume 1) in Section 2.7.5 that M87-092 and M95-300 are two principal controlled trials that demonstrate the efficacy and safety of lansoprazole in relieving the symptoms of non-erosive GERD. They base this conclusion on a brief overview of the three clinical trials in Sections 2.7.2 on Clinical Efficacy (pages 250-264) and Section 2.7.3 on Clinical Safety (pages 265-269). The final statement simply jumps to:

- "Thus we recommend short-term treatment (four to eight weeks) with lansoprazole 30 mg QD for symptomatic relief in patients with gastroesophageal reflux disease."

Comment: This conclusion appeared to be very abrupt, and the arguments for the dose of 30 mg daily appear to be based mainly on statistical interpretations of the re-analysis of M87-092, since there was no comparison of 15 mg and 30 mg daily dosing in the U.K. study D75p501. Both of those older studies showed no advantage of 60 mg/day over 30 mg/day, so the real question comes down to a choice between daily doses of 15 or 30 mg of lansoprazole. The more recent study M95-300, as will be shown in detail, does not support the 30 mg daily dose but strongly indicate 15 mg/day to be preferable.

It may be recalled that the approved dose for healing erosive esophagitis in short-term treatment is 30 mg of lansoprazole for up to 8 weeks, very close to what is now being requested for relief of symptoms in non-erosive esophagitis, 4 to 8 weeks at that dose. Lansoprazole 15 mg/day for up to one year is also approved for maintenance of healing of erosive esophagitis.

It is not easy from the data to understand why the sponsor wishes to ignore the findings of their best study, M95-300, and to rely so much on the nebulous findings of the retrospective re-analyses of the subset of patients in M87-092, a study that was not designed for demonstration of symptom relief and was focussed on healing in patients with erosive esophagitis.

The detailed consideration of the three studies in the following summaries and comments will address principally the dosing issue, which is the main question about this submission and the request of the sponsor for approval of lansoprazole for this indication.

The question of dose goes beyond the daily amount of lansoprazole to be taken to the questions of timing and duration, i.e., to the regimen to be recommended. If the response to lansoprazole is fairly prompt, then what argument can be offered to prolong the treatment for weeks, even if 8 weeks can be considered "short-term." If it is argued that the data support 8 weeks because that is what was done, then it could be said that any duration could be justified simply by extending studies. If it is stated that several weeks (up to 8) are needed so that effects can be sustained, are we then getting into a maintenance claim? If patients respond promptly and continue to do well for 8 weeks on a daily dose of lansoprazole, then what happens when they stop?

D. Controlled Clinical Trials

1. Study M87-092

The original NDA 20-406 contained, as one of the principal studies for the indication of healing erosive esophagitis associated with GERD, a report PPRd/90/003 dated 27 September 1990 on the "Effects of lansoprazole (A-65006) on acute gastroesophageal reflux disease." The report was authored by DE Jennings and PA Greski, and was in the NDA submission of 12 November 1993, 639 volumes, listed in the index as in Volumes 2.191 to 2.198. The study was reviewed by Dr. Hugo Gallo-Torres, mainly for data on healing of the erosions that were seen in 186 (isolated erosions, grade 3, in 155; and confluent erosions, grade 4, in 31) patients. Another 106 patients of the 292 summarized in the report had no erosions, but only friability of the esophageal mucosa with bleeding under instrumentation, grade 2 esophagitis according to the classification system of Kaul, et al. 1986. All 292 patients were reported upon, and intent-to-treat (ITT) analyses were done for 288 of them. Of the 106 who had no erosions, 27 were assigned randomly to placebo, 23 to lansoprazole 15 mg, lansoprazole, and lansoprazole daily for 8 weeks, as tabulated in the review by Dr Gallo-Torres, page 62. Of the 186 patients who had erosive esophagitis, 183 had data for healing after 8 weeks of treatment, as follows:

result	placebo	lanso 15	lanso 30	lanso 60
Healed at 8 weeks (percent)	12/40 (30.0)	40/49 (81.6)	40/47 (85.1)	41/47 (87.2)
Gain over placebo (exact p)		(51.6) <<0.001	(55.1) <<0.001	(57.2) <<0.001
Gain over lanso 15			(3.5) N.S.	(5.6) N.S.

When the 106 patients with no erosions (grade 2) were included, 288 patients had data for ITT analyses, that showed:

result	placebo	lanso 15	lanso 30	lanso 60
Healed at 8 weeks (percent)	31/66 (47.0)	60/72 (83.3)	62/71 (87.3)	70/79 (88.6)
Gain over placebo (exact p)		(36.4) <0.001	(40.4) <0.001	(41.6) <0.001
Gain over lanso 15			(4.0) N.S.	(5.3) N.S.

Comment: Since the 106 had no erosions to start, the apparent healing rates on placebo may have been falsely inflated, so the drug effect would be blunted but still highly significantly favorable for all doses of lansoprazole. Of these, 105 (288-183) had data for ITT analyses, and the difference between considering all 288 with grades 2-4 esophagitis minus the 183 with erosive esophagitis (grades 3 & 4) would give the 8-week healing rates in those with grade 2, non-erosive esophagitis, if all of the patients not shown to be healed were in fact not healed:

result	***placebo***	***lanso 15***	***lanso 30***	***lanso 60***
Healed at 8 weeks (percent)	*19/26 (73.1)*	*20/23 (87.0)*	*22/24 (91.7)*	*29/32 (90.6)*
?Unhealed, 8 weeks	*?7/26*	*?3/23*	*?2/24*	*?3/32*
Observed erosions	*2/26*	*1/23*	*0/24*	*0/32*

Erosions seen in patients endoscoped at 8 weeks who had shown no erosions before randomization to study drug, but only grade 2 esophagitis with friability, may illustrate the point that patients with GERD symptoms can have esophageal erosions that come and go spontaneously (on placebo treatment), i.e., appear to heal and to occur without treatment. The numbers of such patients are very small and differences are not statistically significant.
There did not appear to be any justification for recommending any dose higher than 15 mg/day, since the healing rates were not significantly higher for the 30 or 60 mg/day doses, whether or not the 106 patients were included at 8 weeks. For the whole group of 292 patients when endoscoped earlier, at 6 or 4 weeks, there was no significant advantage of the 30 mg daily dose over the 15 mg dose, in healing rates. There is no question that lansoprazole is effective, only what dose is needed. It is not clear how the dose of 30 mg/day was justified for approval, since it was not recommended by Dr. Gallo-Torres (see his review, page 318).

With respect to ***symptoms****, not the primary aim of the full M87-092 study, patients without erosive esophagitis were not separately analyzed, but symptoms of heartburn were reduced by all three doses significantly superiorly to placebo at 2, 4, and 6 weeks after initiation of treatment.*

The current reanalysis goes back to the M87-092 study, which is proposed by the sponsor as one of two principal studies supporting the requested claim for an indication for treatment of symptomatic GERD, stated by the sponsor (Volume 1 of 55, page 027) as:

> "**Short-Term Treatment of Symptomatic GERD**
> PREVACID Delayed-Release Capsules are indicated for short-term treatment (4 to 8 weeks) for relief of symptoms associated with GERD, including heartburn and abdominal pain."

For the purpose of this supplemental NDA, the sponsor re-analyzed data from Study M87-092 for the 106 patients found at pre-randomization endoscopy to have no esophageal erosions, but only grade 2 esophagitis as indicated by mucosal friability with bleeding under instrumentation within a week prior to initiation of randomized treatment. Patients with Barrett's esophageal changes and

patients with no endoscopically visible abnormalities of the esophageal mucosa (grade 0) or only mucosal edema or hyperemia (grade 1) were not included. Efficacy analyses were based primarily on diary data wherein patients recorded the frequency and severity of day and night GERD symptoms and use of antacid (Gelusil) tablets, and upon symptom assessment by investigators. Diary cards were to be completed daily by patients in M87-092 and summarized biweekly at the time of visits.

Comment: Because it is very important to understand exactly how Study M87-092 was carried out, the amended protocol was found in Volume 7 of this submission (pages 002-043), and is summarized briefly as follows:

Protocol number M87-092 was apparently written originally in 1987, was amended administratively on 21 January 1988 to change dosing to once daily each morning upon arising and before breakfast instead of at bedtime, at approximately 35 study sites to provide at least 260 "complete and acceptable" patients (65 per study arm). No previous gastrointestinal surgical procedures other than simple closure of a perforation were allowed for eligible patients. A further amendment was made 17 June 1988, to specify that all routine laboratory tests would be done by SciCor in Indianapolis, IN, and "expanded" ranges of results acceptable as "normal" were listed (see page 005); the amendment further excluded concurrent drugs such as anticoagulants, hydantoins, theophylline derivatives and benzodiazepines, but "azepams" (lor-, nitr-, ox-, and tem-) were allowed.
The study was characterized as a Phase II, placebo-controlled trial to assess Abbott-65006 (lansoprazole) for the "treatment of reflux esophagitis disease and to assess time to recurrence of esophagitis in patients whose esophagitis is healed." The contract research organization "IBRD" (the Institute for Biological Research and Development, Inc., Irvine, CA) was to conduct the study for the sponsor, Takeda-Abbott.

Patients were to have active esophagitis documented by endoscopy within 7 days of entry into the treatment period, defined by grade 2 to 4 according to Kaul, et al. (1986), including "friability of the mucosa with bleeding under instrumentation" (grade 2), "isolated ulcerations" (grade 3), or "confluent ulcerations" (grade 4), but not simple "mucosal edema and hyperemia (grade 1) or "no abnormalities" (grade 0). It was not specifically stated that the patients had to have symptoms, but the case report form required recording of symptoms. Visits were to be scheduled at 2, 4, 6, and 8 weeks after initiation of treatment. Repeat endoscopy was to be done at week 4, and if not healed then at week 6, and in all cases at week 8. If complete healing of the esophageal mucosa (to grades 1 or 0) was observed at week 8, patients were to be treated for another 6 months, with visits at 1, 3, and 6 months or when symptoms of esophagitis recurred. Those not healed at 8 weeks were not to be continued for further study. Selected investigators were asked to obtain gastric mucosal biopsies from the greater curvature mucosa in approximately 100 patients for estimation of enterochromaffin-like cell density; this was to be repeated at the week 8 endoscopy, and at post study months 1,3, and 6 if healed at study week 8. Patients were provided two bottles of blinded medication containing either placebo, 7.5 or 15 mg of lansoprazole, and could receive 4 placebo, 2 lansoprazole 7.5 or 15 mg and 2 placebo, or 4 lansoprazole 15 mg, to provide daily doses of 0, 15, 30, or 60 mg. Patients were instructed to keep a daily diary of symptoms, dosing information,

Gelusil tablets used, concurrent medicines, and missed doses, to be collected at biweekly visits.

Study M87-092 was carried out from February 1988 to June 1989, by 34 investigators who enrolled 292 patients (195 men, 97 women) with grade 2 (106), 3 (155), or 4 (31) esophagitis. Of the 292 patients, 106 (56 men, 50 women) at 27 centers had only grade 2 esophagitis when endoscoped before the study.

	Grade 2	Grade 3 or 4
Richard Aronson, M.D. (2925), Chicago Heights IL	6M/7F	
John Allen, M.D. (2926), Minneapolis MN		8M/0F
Dennis Avner, M.D. (3094), Salt Lake City UT		7M/3F
William Berry, M.D. (2927), Longmont CO	4M/0F	8M/2F
Donald Bruns, M.D. (2928), Red Wing MN	3M/3F	7M/0F
James Cozzarelli, M.D. (2930), Lansdale PA	2M/1F	
Jeffrey Davis, M.D. (2931), Madison WI	2M/2F	2M/4F
Ernst Dorsch, M.D. (3095), Houston TX	7M/5F	4M/2F
David Earnest, M.D. (2933), Tucson AZ	2M/1F	6M/1F
William Erfling, M.D. (2934), Boulder CO	4M/2F	6M/0F
Richard Fisher, M.D. (2935), Modesto CA	3M/3F	5M/3F
Duane Fitch, M.D. (2936), Wilson NC	0M/2F	1M/3F
Terrence Hill, M.D. (2938), Corvallis OR		1M/5F
Richard Houston, M.D. (2937), Rockford IL		4M/0F
James Jones, M.D. (2940), Ruston LA	1M/2F	5M/7F
George Koval, M.D. (2965), Vancouver WA	0M/2F	3M/2F
James Mertesdorf, M.D. (2941), Charlotte NC	2M/0F	3M/0F
Rao Movva, M.D. (2942), Moline IL	4M/2F	6M/0F
David Nano, M.D. (2943), Sunnyvale CA		2M/1F
Joseph Nelson III, M.D. (2945), Salem VA	5M/3F	1M/0F
Kent Nelson, M.D. (2947), Bountiful UT		4M/3F
Jacob Neuman, M.D. (2944), Flushing NY	0M/1F	0M/3F
Michael Oliver, M.D. (2948), Covina CA	1M/0F	1M/0F
Richard Rafoth, M.D. (2949), Everett WA	1M/0F	6M/3F
J. David Rowekamp, M.D. (2950), Winona MN		4M/1F
Bruce Sahba, M.D. (2951), San Diego CA	2M/4F	10M/1F
Jerrold Schwartz, M.D. (2953), Arlington Heights IL	2M/2F	6M/0F
Charles Scowcroft, M.D. (2954), Anderson SC	0M/1F	4M/1F
Bavikatte Shivakumar, M.D. (2955), Davenport IA	0M/1F	8M/1F
Timothy Simmons, M.S. (2956), Inglewood CA	0M/2F	4M/4F
Ronald Thune, M.D. (2957), Green Bay WI	3M/2F	8M/2F
Robert Wagner, M.D. (2958), Oconomowoc WI	1M/0F	2M/0F
John Whitaker, M.D. (2959), Shreveport LA	1M/1F	
Robert Wintroub, M.D. (3096), Inglewood CA	0M/1F	1M/0F
TOTALS	56M/50F	136M/50F

REANALYSES OF THE SUBSET OF 106 PATIENTS WITH NON-EROSIVE ESOPHAGITIS

Of the 34 investigators, 27 listed above enrolled from 1 to 13 patients with grade 2 esophagitis, in total 106 patients, who were randomized to placebo (27), lansoprazole 15 (23), lansoprazole 30 (24) and lansoprazole 60 mg (32). The randomized groups did not differ significantly in gender, race , alcohol/caffeine/tobacco, age, weight/height adjusted for gender (Table 7.4.2, Vol. 4, page 137-8).

Comment: The justification for the study size was not provided in the protocol, but in the report (Volume 4, page 034) was stated to be based on a 99% chance to detect difference between placebo and lansoprazole groups if true ***healing*** *rates were 50% and 85%. The principal outcome measure was to be the proportion of patients showing healing to grade 1 or 0, at weeks 4 and 8. Secondary analyses of pain scores and antacid use at 2, 4, 6, and 8 weeks, and recurrence rates at 8 weeks for those healed at 4 or 6 weeks, were also planned, as well as a 6-month follow-up study in patients healed at 8 weeks. Symptom analysis was not a primary goal of Study M87-092, but data were collected, in patient daily diaries and investigators' biweekly assessments of what patients told them.*

Primary symptoms of reflux esophagitis were taken as heartburn, burning in the upper abdomen, belching, gastroesophageal regurgitation, and painful swallowing. Other symptoms were also noted, including fullness/bloating/early satiety, abdominal distension, anorexia, nausea, vomiting, day abdominal pain, night abdominal pain, flatulence, abdominal rumbling, diarrhea, constipation, hematemesis, and melena.

Symptoms were scored as 3 for severe, 2 for moderate, 1 for mild, and 0 for none. Mild symptoms were defined as those not lasting long or easily tolerated; moderate symptoms as those that caused discomfort and interrupted usual activities, and severe symptoms those which caused great interference with usual activities and may have been incapacitating (see page 031, Volume 4). The symptoms were assessed and graded by the investigators for the 2-week preceding period. Diaries were collected at each biweekly visit, and average scores entered by the patients were calculated. The same 0 to 3 scale was used by the patients. Average daily severity scores were calculated and percentages of days with each symptom and use of Gelusil, and average number of Gelusil tablets used were calculated for pairwise treatment group comparisons using the Wilcoxon two-sample test during the first 4 weeks and over the entire 8-week period (see Volume 1, page 254).

Two patients had insufficient data for analysis even by intent-to-treat: Sahba #3317, a 24-year-old white woman randomized to lansoprazole 60 mg/day did not record any diary data, and Fisher #3365, a 58-year-old white woman randomized to placebo was excluded because of abnormal pre-study laboratory results and received only 9 days of placebo treatment. The sponsor also excluded for "evaluable" analyses two other patients who received less than 14 days of study drug: Dorsch #3729, a 41-year-old hispanic woman randomized to lansoprazole 60, and J. Nelson #3202, a 51-year-old woman randomized to placebo. There were other deviations from protocol, including endoscopies done more than a week before starting drug treatment (8-11 days, instead of not more than 7), randomization number assigned out of sequence, unauthorized use of other medications including metoclopramide and histamine receptor-2 antagonists, and excessive used of analgesics.

The most prevalent pre-study symptom was heartburn, reported in 94 of the 106 patients, followed by upper abdominal burning in 90, belching in 80, gastroesophageal regurgitation in 73, and painful swallowing in 34 of the patients. Although the average severity of heartburn was higher in the group of 23 randomized to receive lansoprazole 15 mg/day (2.06), it was not significantly more than the mean severity in the 27 on placebo (1.67), the 24 on lansoprazole 30 mg (1.50), or the 32 on lansoprazole 60 mg/day (1.69), as shown in Table 7.4.4 on page 140 of Volume 4.

Of the 106 patients with grade 2 esophagitis at baseline, 11 withdrew from the study prematurely, and 3 developed erosive esophagitis by week 8; 79 patients were both healed and willing to continue into the post-study(16 who had been on placebo and 63 on various doses of lansoprazole), 13 did not continue.

	Total	placebo	lanso 15	lanso30	lanso 60
Enrolled	106	27	23	24	32
Screening labs	-1	-1			
Adverse events	-3	-1		-1	-1
Rx failure	-2	-1			-1
Lost to followup	-4		-1	-1	-2
Other	-1		-1		
Completed study	95	24	21	22	28
"Evaluable" diaries	102	25	23	24	30
ITT diary data	104	26	23	24	31

Results of diary data analyses for the 102 "evaluable" and 104 "ITT" patients are presented by the sponsor in Tables 8.1.1 to 8.1.4 in Volume 4, pages 145-52. The results are very similar, so the ITT results will be discussed. The diary data were analyzed for the average pain severity/day, the percentage of days with pain, separately for day pain and night pain, and separately for the first 4 weeks and for the whole 8 weeks, and for Gelusil tablet use, both number/day and percent of days.

Comment: This retrospective analysis of this study planned in 1987 is notable for both what it reports and what is not reported. The sponsor has selected certain symptoms, both those assessed daily by the patients in their diaries and those evaluated at biweekly visits by the investigators who asked how the patients were doing. It is not clearly stated that symptom assessment at weeks 4, 6, and 8 would not have been done by the investigators after they looked at the esophageal mucosa by endoscopy. Symptom assessment at 2 weeks could not possibly have been so confounded, since no endoscopies were done then, and it would be hoped that symptoms would have responded mostly by that time anyway. It is long to wait for symptom relief in 4, 6, or 8 weeks, particularly if the symptoms were severe or even moderately severe. It is notable that five of the eight symptoms originally classified as "primary" for GERD in the protocol have been selected in this retrospective analysis for re-analysis: upper abdominal burning, heartburn, painful swallowing, belching, regurgitation. This raises questions of "data-dredging", and if results should be considered new hypotheses to be tested prospectively, rather than as a principal, "pivotal" trial.

For the first 4 weeks of the study:

Daytime abdominal pain (ITT)

		average pain severity		p-values	
placebo	26	0.52 ± 0.40	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.28 ± 0.30	***0.025***		
lanso 30	24	0.16 ± 0.17	***<0.001***	*0.189*	
lanso 60	31	0.31 ± 0.39	***0.018***	*0.826*	*0.351*

		percent of days with pain		p-values	
placebo	26	33.6 ± 21.8	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	19.6 ± 18.0	***0.044***		
lanso 30	24	12.8 ± 12.8	***<0.001***	*0.185*	
lanso 60	31	19.5 ± 22.3	***0.009***	*0.586*	*0.426*

Nighttime abdominal pain (ITT)

		average pain severity		p-values	
placebo	26	0.44 ± 0.35	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.27 ± 0.30	*0.100*		
lanso 30	24	0.16 ± 0.15	***0.004***	*0.287*	
lanso 60	31	0.25 ± 0.30	***0.021***	*0.451*	*0.758*

		percent of nights with pain		p-values	
placebo	26	28.4 ± 18.7	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	19.0 ± 17.7	*0.123*		
lanso 30	24	12.8 ± 11.2	***0.005***	*0.312*	
lanso 60	31	17.5 ± 21.7	***0.016***	*0.390*	*0.918*

Antacid (Gelusil) use/24 hours (ITT)

		average number of tablets		p-values	
placebo	26	1.23 ± 1.19	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.50 ± 0.66	***0.005***		
lanso 30	24	0.37 ± 0.62	***0.001***	*0.669*	
lanso 60	31	0.45 ± 0.65	***0.002***	*0.993*	*0.645*

		percent of days used		p-values	
placebo	26	30.1 ± 22.1	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	15.4 ± 16.4	***0.012***		
lanso 30	24	13.0 ± 13.3	***0.002***	*0.957*	
lanso 60	31	15.2 ± 19.0	***0.006***	*0.965*	*0.939*

For the whole 8 weeks of the study:

Daytime abdominal pain (ITT)

		average pain severity	*p-values*		
placebo	26	0.87 ± 0.71	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.46 ± 0.51	***0.041***		
lanso 30	24	0.27 ± 0.28	***0.001***	*0.213*	
lanso 60	31	0.44 ± 0.48	***0.014***	*0.827*	*0.272*

		percent of days with pain	*p-values*		
placebo	26	56.0 ± 35.4	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	32.7 ± 32.0	***0.031***		
lanso 30	24	21.5 ± 22.9	***0.001***	*0.205*	
lanso 60	31	29.7 ± 29.1	***0.006***	*0.786*	*0.372*

Nighttime abdominal pain (ITT)

		average pain severity	*p-values*		
placebo	26	0.75 ± 0.72	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.45 ± 0.52	*0.155*		
lanso 30	24	0.26 ± 0.25	***0.008***	*0.292*	
lanso 60	31	0.37 ± 0.40	***0.037***	*0.534*	*0.569*

		percent of nights with pain	*p-values*		
placebo	26	47.7 ± 35.7	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	31.0 ± 30.4	*0.109*		
lanso 30	24	21.4 ± 20.9	***0.012***	*0.302*	
lanso 60	31	26.6 ± 27.9	***0.031***	*0.552*	*0.818*

Antacid (Gelusil) use/24 hours (ITT)

		average number of tablets	*p-values*		
placebo	26	2.00 ± 1.82	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.73 ± 0.92	***0.005***		
lanso 30	24	0.73 ± 1.48	***0.001***	*0.881*	
lanso 60	31	0.74 ± 0.95	***0.003***	*1.000*	*0.959*

		percent of days used	*p-values*		
placebo	26	49.9 ± 34.8	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	24.8 ± 28.8	***0.014***		
lanso 30	24	22.0 ± 23.9	***0.004***	*0.907*	
lanso 60	31	25.1 ± 29.4	***0.008***	*0.972*	*0.851*

Comment: Very similar tabulations for the 102 "evaluable" subset were submitted for the 4-week and 8-week results (Volume 4, Table 8.1.1, pages 145-6;Table 8.1.3, pages 145-6).

For the first 4 weeks of the study:

Daytime abdominal pain (evaluable 102)

		average pain severity		*p-values*	
placebo	25	0.51 ± 0.41	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.28 ± 0.30	***0.032***		
lanso 30	24	0.16 ± 0.17	***0.001***	*0.189*	
lanso 60	30	0.26 ± 0.30	***0.012***	*0.665*	*0.456*

		percent of days with pain		*p-values*	
placebo	25	32.0 ± 20.8	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	19.6 ± 18.0	*0.066*		
lanso 30	24	12.8 ± 12.8	***0.001***	*0.185*	
lanso 60	30	16.8 ± 16.8	***0.007***	*0.444*	*0.545*

Nighttime abdominal pain (evaluable 102)

		average pain severity		*p-values*	
placebo	25	0.44 ± 0.36	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.27 ± 0.30	*0.124*		
lanso 30	24	0.16 ± 0.15	***0.006***	*0.287*	
lanso 60	30	0.22 ± 0.26	***0.013***	*0.326*	*0.916*

		percent of nights with pain		*p-values*	
placebo	25	27.2 ± 18.1	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	19.0 ± 17.7	*0.176*		
lanso 30	24	12.8 ± 11.2	***0.007***	*0.312*	
lanso 60	30	14.8 ± 15.6	***0.012***	*0.276*	*0.916*

Antacid (Gelusil) use/24 hours (evaluable 102)

		average number of tablets		*p-values*	
placebo	25	1.25 ± 1.21	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.50 ± 0.66	***0.006***		
lanso 30	24	0.37 ± 0.62	***0.001***	*0.669*	
lanso 60	30	0.39 ± 0.56	***0.001***	*0.843*	*0.779*

		percent of days used		*p-values*	
placebo	25	29.6 ± 22.4	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	15.4 ± 16.4	***0.018***		
lanso 30	24	13.0 ± 13.3	***0.004***	*0.957*	
lanso 60	30	13.1 ± 15.4	***0.004***	*0.871*	*0.896*

For the whole 8 weeks of the study:

Daytime abdominal pain (evaluable 102)

		average pain severity		*p-values*	
placebo	25	0.87 ± 0.72	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.46 ± 0.51	***0.048***		
lanso 30	24	0.27 ± 0.28	***0.001***	*0.213*	
lanso 60	30	0.40 ± 0.43	***0.009***	*0.679*	*0.359*

		percent of days with pain		*p-values*	
placebo	25	55.4 ± 36.0	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	32.7 ± 32.0	***0.040***		
lanso 30	24	21.5 ± 22.9	***0.001***	*0.205*	
lanso 60	30	27.4 ± 26.4	***0.004***	*0.627*	*0.479*

Nighttime abdominal pain (evaluable 102)

		average pain severity		*p-values*	
placebo	25	0.76 ± 0.73	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.45 ± 0.52	*0.170*		
lanso 30	24	0.26 ± 0.25	***0.010***	*0.292*	
lanso 60	30	0.34 ± 0.38	***0.028***	*0.429*	*0.707*

		percent of nights with pain		*p-values*	
placebo	25	47.4 ± 36.4	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	31.0 ± 30.4	*0.122*		
lanso 30	24	21.4 ± 20.9	***0.017***	*0.302*	
lanso 60	30	24.2 ± 24.8	***0.021***	*0.414*	*0.979*

Antacid (Gelusil) use/24 hours (evaluable 102)

		average number of tablets		*p-values*	
placebo	25	2.04 ± 1.84	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	0.73 ± 0.92	***0.005***		
lanso 30	24	0.73 ± 1.48	***0.001***	*0.881*	
lanso 60	30	0.69 ± 0.92	***0.002***	*0.878*	*0.889*

		percent of days used		*p-values*	
placebo	25	50.2 ± 35.4	*vs. placebo*	*vs.lanso 15*	*vs lanso 30*
lanso 15	23	24.8 ± 28.8	***0.015***		
lanso 30	24	22.0 ± 23.9	***0.005***	*0.907*	
lanso 60	30	23.4 ± 28.3	***0.005***	*0.892*	*0.701*

Comment: Results for the subset of 102 "evaluable" patients are virtually indistinguishable from those for the 014 "ITT" patients. It make no difference which set the sponsor may wish to use in support of the labeling; the reproduction of the evaluable subset in the text of the report (pages 052-053) may suggest that the sponsor wishes to use those data for the labeling.

The sharp rise in the percentage of days with pain, particularly in the placebo group, in the data for the whole 8 weeks compared to the first 4 weeks, suggests that something unfavorable is going on in the second 4 weeks. For the evaluable subset, day abdominal pain was reported in diaries in 33.3% of the first 4 weeks, or on 9.3 days, while for the whole 8 weeks in 66.7% or 37.3 days. This means that in the second 4 weeks pain was reported ***every one of the 28 days****, in those on placebo! This was not so strikingly true for patients on lansoprazole, where pain was reported on 3.1 days during the first 4 weeks, and on 7.4 of the 28 days in the second 4 weeks in those taking lansoprazole 15 mg/day, from 2.5 of the first 28 days to 2.9 of the second 28 days on lansoprazole 30 mg/day, and from 3.1 of the first 28 to 7.1 of the second 28 days on lansoprazole 60 mg/day. The same thing was true for night abdominal pain, and to some extent for need to take Gelusil tablets for relief.*

Heartburn is widely accepted as the cardinal symptom of GERD, and it was found in the retrospective analyses of M87-092 to be so. It was the most prevalent of the symptoms considered, and was reported by 94 of the 106 patients with non-erosive GERD who are the focus of this study reanalysis. Second to it was "burning in the upper abdomen" in 90 of the 106, but it was not made clear exactly what was the distinction between these two symptoms, as reported to and evaluated by the investigators at the biweekly visits. The data for the five symptoms (burning upper abdomen, heartburn, painful swallowing, belching, and gastroesophageal regurgitation) are presented in the submitted Tables 8.2.1 to 8.2.8, pages 153-192, Volume 4. Of the five symptoms, only the first two showed significant treatment effects of lansoprazole in any dose compared to placebo, either for the evaluable subset of 102 patients or for 105 who in this analysis were called "ITT" (excluding only patient Sahba #3317 for whom no data were available after the baseline; see Appendix E.10.A, page 337, Volume 5). Analyses of the five symptoms for both evaluable and ITT groups were done for investigator evaluations at 2, 4, 6, and 8 weeks. In addition, the sponsor calls attention to analyses of 288 ITT patients and 253 evaluable patients from the original study that also included patients with erosive esophagitis grades 3 & 4, for other symptoms of fullness/bloating/early satiety, abdominal distension, anorexia, nausea, vomiting, day abdominal pain, night abdominal pain, flatulence/abdominal rumbling, diarrhea, constipation, hematemesis, and melena (Appendix D.2.1 and D.2.2., pages 004-027, Volume 5), at 8 weeks compared to baseline. Of these symptoms, only the day and night pain were suggestive of significant benefit from lansoprazole over placebo.

Of perhaps special interest, as indicated by the sponsor in the text of the re-analysis report in Table 8.2.a on page 054 of Volume 4, all three doses of lansoprazole showed statistically significant improvement in symptoms of heartburn and burning in the upper abdomen at week 2, for upper abdominal burning at week 4, while the two higher doses of lansoprazole gave statistically significant results also at week 6 for those two symptoms and for regurgitation at weeks 2 and 4. The search for statistically significant findings was the focus of the report on pages 053-6.

Comment: Emphasis was placed on results at week 8, compared to baseline, by bar-graphic representation of the five "primary" symptoms treated on the four regimens (page 057, Volume 4). It is apparent from those bar graphs that severe symptoms of upper abdominal burning and heartburn were most prevalent in the sub-group of patients randomized to lansoprazole 15 mg/day, so they chanced to have somewhat more severe disease at baseline than the other three treatment groups. In numerical terms, the 23 patients in the lanso 15 group averaged heartburn scores of 2.09 in the 102 patients of the evaluable set, compared to 1.50 in the 24 in the lanso 30 group, 1.63 in the 30 in the lanso 60 group, and 1.68 in the 25 in the placebo group, but the difference was not significant (p=0.169), as shown on page 139, Volume 4.

It may be argued that symptom relief might be expected and very much desired by patients in less than 8 weeks; in fact, even 2 weeks is a considerable time to wait for relief of severe, disabling heartburn, as grade 3 symptoms are defined, or moderately severe heartburn that interferes with life activities and enjoyment. The investigators first saw the patients after 2 weeks on treatment, and patients described their symptom severity over the previous 2-week period. It is possible that relief or improvement in symptoms may have occurred more promptly, within a few days after initiation of lansoprazole treatment, but that is not brought out in these analyses. Only the diary data could be used to address this issue of how quickly some patients were relieved or improved. The closest approximation to this are the data for 2-week responses displayed for 105 ITT patients in Table 8.2.2 (page 159, Volume 4):

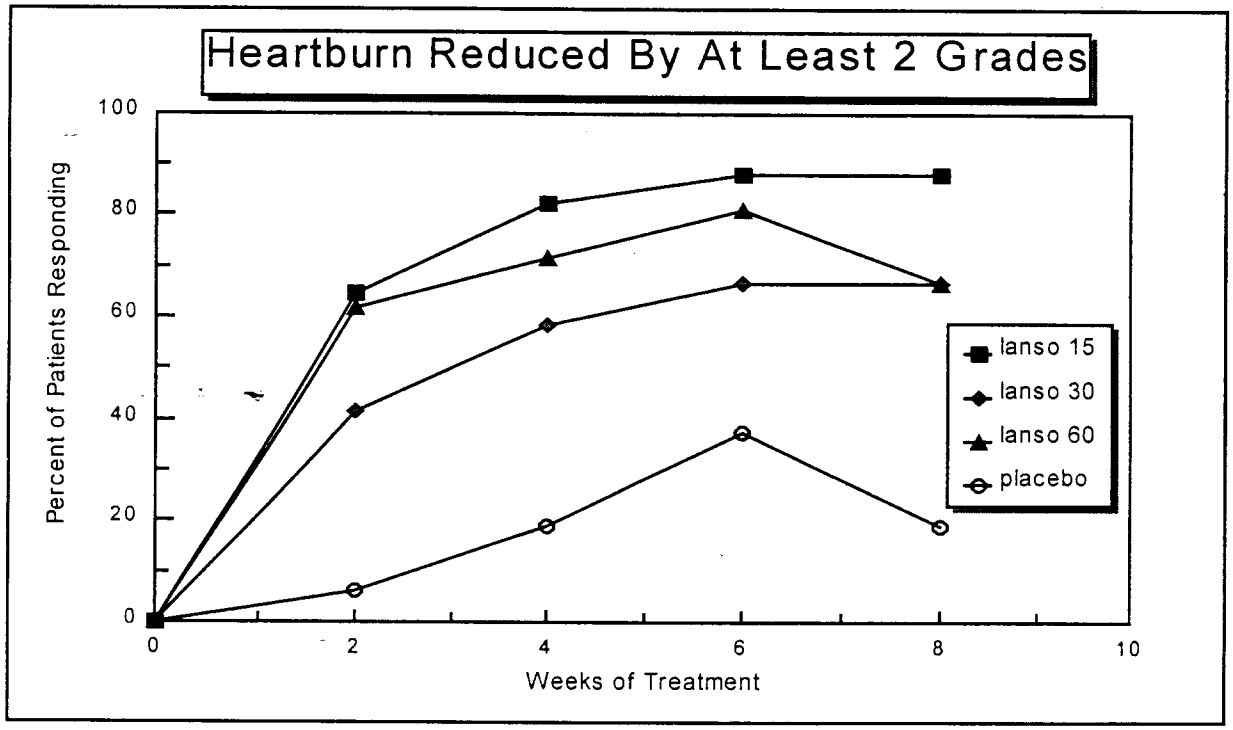
HEARTBURN AT WEEK 2: 105 ITT PATIENTS WITH NON-EROSIVE ESOPHAGITIS

	treatment	heartburn severity after 2 weeks of treatment					
		n	*none*	*mild*	*moderate*	*severe*	*mean*
Baseline: **Severe**	placebo	6	**1**	**0**	2	3	2.17
(24)	lanso 15	9	**3**	**4**	1	1	1.00
	lanso 30	2	**0**	**1**	1	0	1.50
	lanso 60	7	**4**	**1**	1	1	0.86
Moderate	placebo	8	**0**	2	6	0	1.75
(40)	lanso 15	8	**4**	4	0	0	0.50
	lanso 30	10	**4**	5	1	0	0.70
	lanso 60	14	**7**	3	3	1	0.86
Mild	placebo	9	2	5	2	0	1.00
(29)	lanso 15	5	5	0	0	0	0.00
	lanso 30	10	7	3	0	0	0.30
	lanso 60	5	4	1	0	0	0.20
None	placebo	3	3	0	0	0	0.00
(12)	lanso 15	1	1	0	0	0	0.00
	lanso 30	2	2	0	0	0	0.00
	lanso 60	6	5	1	0	0	0.17

The sponsor's analysis of these changes across all four baseline severity strata, using Cochran-Mantel-Haenszel (CMH) methods that generate Q values from which p values can be obtained, shows that all three lansoprazole regimens gave significantly superior results compared to placebo, but none of the lansoprazole regimens were significantly different from each other:

placebo vs lanso 15	Q(CMH) = 16.29	$p < 0.001$
placebo vs lanso 30	Q(CMH) = 12.09	$p = 0.001$
placebo vs lanso 60	Q(CMH) = 9.86	$p = 0.002$
lanso 15 vs lanso 30	Q(CMH) = 2.00	$p = 0.158$
lanso 15 vs lanso 60	Q(CMH) = 0.41	$p = 0.522$
lanso 30 vs lanso 60	Q(CMH) = 0.00	$p = 0.951$

Comment: Even though the numbers of patients in each group are relatively small, these results generate a quite impressive hypothesis that lansoprazole treatment very significantly reduces heartburn within 2 weeks. The data do not provide support for a particular dose of lansoprazole, since none is significantly better than the lowest dose used, 15 mg/day. The data do not provide an optimum regimen, since 2 weeks elapsed on treatment before the questions were asked. Another way of looking at these data, from the standpoint of a patient with symptoms, is that the most important thing is to obtain as prompt as possible and substantial relief of the more severe levels of heartburn symptoms. If it is postulated that most patients would accept a change from moderate to none, or from severe to mild or none, as significant clinical benefit, then the data can be analyzed for decrease of at least two grades of severity of heartburn within 2 weeks on treatment:



Using the ITT set of 105 patients (page 159), it may been seen that 24 of them had severe heartburn, grade 3, before the study, and another 40 had moderately severe heartburn before the study. Very similar are the data for 101 evaluable patients in Table 8.2.1 (page 154). If one focusses on what patients want, it would undoubtedly be substantial and rapid improvement of severe or moderately severe symptoms of heartburn. If one considers the above text table of heartburn at 2 weeks in the 105 ITT patients, and asks "in how many of the 64 patients with moderate or severe heartburn did treatment reduce the symptoms by at least two grades within two weeks," it may be seen that this was noted in the following numbers of patients:

placebo	*1/14*	*(6.3%)*
lanso 15	*11/17*	*(64.7%)*
lanso 30	*5/12*	*(41.7%)*
lanso 60	*12/21*	*(57.1%)*

This may be extended to the similar tabulated displays for 4, 6, and 8 weeks (see pages 169, 179, and 189 of Volume 4), to obtain the data plotted in the figure above, which displays the results in a manner perhaps easier to appreciate. It is obvious that statistics are not needed to see that all of the lansoprazole-treated groups did substantially better than those on placebo, that the lansoprazole dose was not a major factor, that the lowest lansoprazole dose was at least as good as higher doses, and that most of the patients responded in this clearly beneficial way within 2 weeks, and only a few more responded after an additional 2 weeks.

Data available in this submission do not include diary data in detail day by day (see Appendix E.9.A, Part 1 for day and night pain, and Gelusil tablet use, pages 282-303, Volume 5; and Appendix E.10.A, Part 1 for heartburn and seven other symptom severity), but only by dates of approximate study visits. In an abstract published in 1996, it was conceded that "abdominal pain" was a n misnomer used inadvertently for reference to all symptoms of GERD (Dorsch, et al., 1996)

The sponsor concludes the report (see page 060, Volume 4) of the re-analysis of M87-092 for the 106 patients with initially non-erosive esophagitis with principal focus upon the patients' diary data on day and night abdominal pain and use of Gelusil tablets. It is stated that the 30 and 60 mg/day lansoprazole regimens over 4 and 8 weeks provided significantly greater relief of day and night pain, and resulted in significant reduction in the need for antacid tablets.

This conclusion is reiterated in the summary Volume 1 (page 256), where it is stated that lansoprazole 30 and 60 mg/day were superior to placebo in reducing day and night abdominal pain and reducing Gelusil tablet use over the first 4 weeks and over the whole 8 weeks. It is further stated that lansoprazole 15 mg was not significantly different from placebo in reducing the percentage of days and nights with pain over these two periods.

Comment: Emphasis on p-values in reaching these conclusions appears erroneous. The numbers were relatively small; failure to show a p-value <0.05 does not necessarily allow this conclusion.