CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020406/S016

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

13.0 PATENT INFORMATION

We, TAP Holdings Inc. (TAP), certify that the drug lansoprazole is claimed in U.S. Patents as listed below. Takeda Chemical Industries, Ltd., of Japan has licensed lansoprazole as covered by these patents to TAP.

U.S. Patent No.	Expiration Date	Coverage
4,628,098	07/29/05	Compound
4,689,333	07/29/05	Pharmaceutical formulations containing lansoprazole, and a method of treating gastritis
5,013,743	02/12/10	Use of lansoprazole for combatting diseases caused by the genus *Campylobacter*
5,026,560	06/25/08	Formulation (spherical granules)
5,045,321	09/03/08	Formulation (spherical granules or tablets stabilized with inorganic salt)
5,093,132	09/03/08	Formulation stabilized with inorganic salt

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-406/S-016

Name of Drug: Prevacid (lansoprazole) Delayed-Release Capsules

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): March 9, 1998

Receipt Date(s): March 10, 1998

Background and Summary Description: NDA 20-406/S-016, submitted December 20, 1996, provides for a new indication: short-term treatment of symptomatic gastroesophageal reflux disease (GERD). This supplement was approvable on February 18, 1998 pending final printed labeling (FPL).

The sponsor has submitted FPL, dated March 9, 1998, in response to the February 18, 1998 approvable letter.

Review

The submitted FPL, dated March 9, 1998, was compared to the original draft labeling, dated December 20, 1996, and to the labeling revisions recommended in the December 22, 1997 and February 18, 1998 approvable letters (attached) as well as the labeling revisions recommended in the March 3, 1998 memorandum of telecon (attached).

No differences were noted. However, the sponsor should be asked to make the following editorial revisions at the next printing of the package insert:

A. 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.*"

B. 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.*"

Conclusions

Supplement 016 should be approved based on the submitted FPL. However, the sponsor should be asked to incorporate the above editorial revisions at the next printing of the package insert.

/S/ 3/11/98

APPEARS THIS WAY
ON ORIGINAL

Maria R. Walsh, M.S.
Project Mangager

Attachments

cc:
Original NDA 20-406/S-016
HFD-180/Div. Files
HFD-180/J.Senior
HFD-180/M.Walsh

3/11/98 concur /S/

Drafted: M.Walsh 3/11/98
r/d Initials: J.Senior
L.Talarico /S/ 3-11-98
Final: M.Walsh
filename: 20406S16.r4

CSO REVIEW

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: March 3, 1998

APPLICATION NUMBER: NDA 20-406/S-016; Prevacid (lansoprazole) Delayed-Release Capsules

BETWEEN:

Name: Judy Decker Wargel, Regulatory Affairs
Phone: (847) 317-5781
Representing: TAP Holdings, Inc.

AND

Name: Maria R. Walsh, M.S., Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Revised Draft Labeling

BACKGROUND: This supplement, submitted on December 20, 1996, provides for a new indication: the treatment of symptomatic gastroesophageal reflux disease (GERD). Approvable letters were issued on December 22, 1997 (requesting revised draft labeling) and February 18, 1998 (requesting final printed labeling). The sponsor submitted a February 20, 1998 amendment which included a proposal for revising the draft labeling to include the efficacy data for frequency of heartburn and a revision to the graphs depicting the efficacy results for the severity of heartburn in the CLINICAL STUDIES section.

Ms.Wargel and Dr. Dennis Jennings, TAP Statistician, called me on March 2, 1998 and relayed that they spoke with Dr. John Senior, medical reviewer, over the weekend at a professional meeting in Phoenix, Arizona. The conversation included a brief discussion of the first day data and the February 20th amendment in which Dr. Senior advised Ms. Wargel and Dr. Jennings that the proposed revisions to the graphs depicting the efficacy results for the severity of heartburn are not acceptable. In the interest of facilitating the review of this amendment, Ms. Wargel relayed that the sponsor is hereby committing to retraction of the revised graphs as they appear in the February 20, 1998 amendment and reinstatement of the graphs as they appeared in the original supplement (i.e. Figures 8.1.1.a and 8.1.1.b).

TODAY'S CALL: After speaking with Dr. Senior, I called Ms. Wargel and informed her that the draft labeling should be revised as follows:

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.

The intent-to-treat analyses demonstrated significant reduction in frequency and severity of day and night heartburn. Data for frequency and severity for the 8-week treatment period were as follows:

Frequency of Heartburn

Variable	Placebo (n=43)	PREVACID 15 mg (n=80)	PREVACID 30 mg (n=86)
		Median	
% of Days without Heartburn			
Week 1	0%	71%*	46%*
Week 4	11%	81%*	76%*
Week 8	13%	84%*	82%*
% of Nights without Heartburn			
Week 1	17%	86%*	57%*
Week 4	25%	89%*	73%*
Week 8	36%	92%*	80%*

*($p<0.01$) vs placebo

(Note to sponsor: Insert Figures 8.1.1.a and 8.1.1.b from the original supplement and not the revised Figures as submitted in the February 20, 1998 amendment.)

I told Ms. Wargel that no revisions to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections as specified in the December 22, 1997 approvable letter are necessary.

Ms. Wargel agreed to the above revisions to the CLINICAL STUDIES section of the proposed labeling and will submit final printed labeling according to the December 22, 1997 and February 18, 1998 approvable letters and this telephone conversation. The call was then concluded.

/S/ 3/4/98

APPEARS THIS WAY
ON ORIGINAL

Maria R. Walsh, M.S.
Project Manager

cc: Original NDA 20-406/S-016
HFD-180/Div. File
HFD-180/M.Walsh
HFD-180/J.Senior
L.Talarico
filename: 20406S16.t2

TELECON

APPEARS THIS WAY
ON ORIGINAL

Division of Gastrointestinal & Coagulation Drug Products

lr 1-7-98

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-406/SE1-016

Name of Drug: Prevacid (lansoprazole) Delayed-Release Capsules

Sponsor: TAP Holdings Inc.

Material Reviewed

Submission Date(s): January 5, 1998

Receipt Date(s): January 6, 1998

Background and Summary Description: NDA 20-406/S-016, submitted December 20, 1996, provides for a new indication: short-term treatment of symptomatic gastroesophageal reflux disease (GERD). This supplement was approvable on December 22, 1997 pending submission of revised draft labeling.

The sponsor has submitted revised draft labeling, dated January 5, 1998, in response to the December 22, 1997 approvable letter.

Review

The submitted revised draft labeling, dated January 5, 1998, was compared to the original draft labeling, dated December 20, 1996 and the revisions recommended in the December 22, 1997 approvable letter. No differences were noted except for the additional information (efficacy results) which was requested in the approvable letter. That additional information is as follows.

> Under CLINICAL STUDIES, **Gastroesophageal Reflux Disease (GERD)**, *Symptomatic GERD*:
>
> The following paragraph was added to this section.
>
> > "The intent-to-treat analysis 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.

Data for the 8-week treatment period were as follows:" (see graphs attached).

Conclusions

The additional information added in the CLINICAL STUDIES, **Gastroesophageal Reflux Disease (GERD)**, *Symptomatic GERD* section must be reviewed by the medical officer.

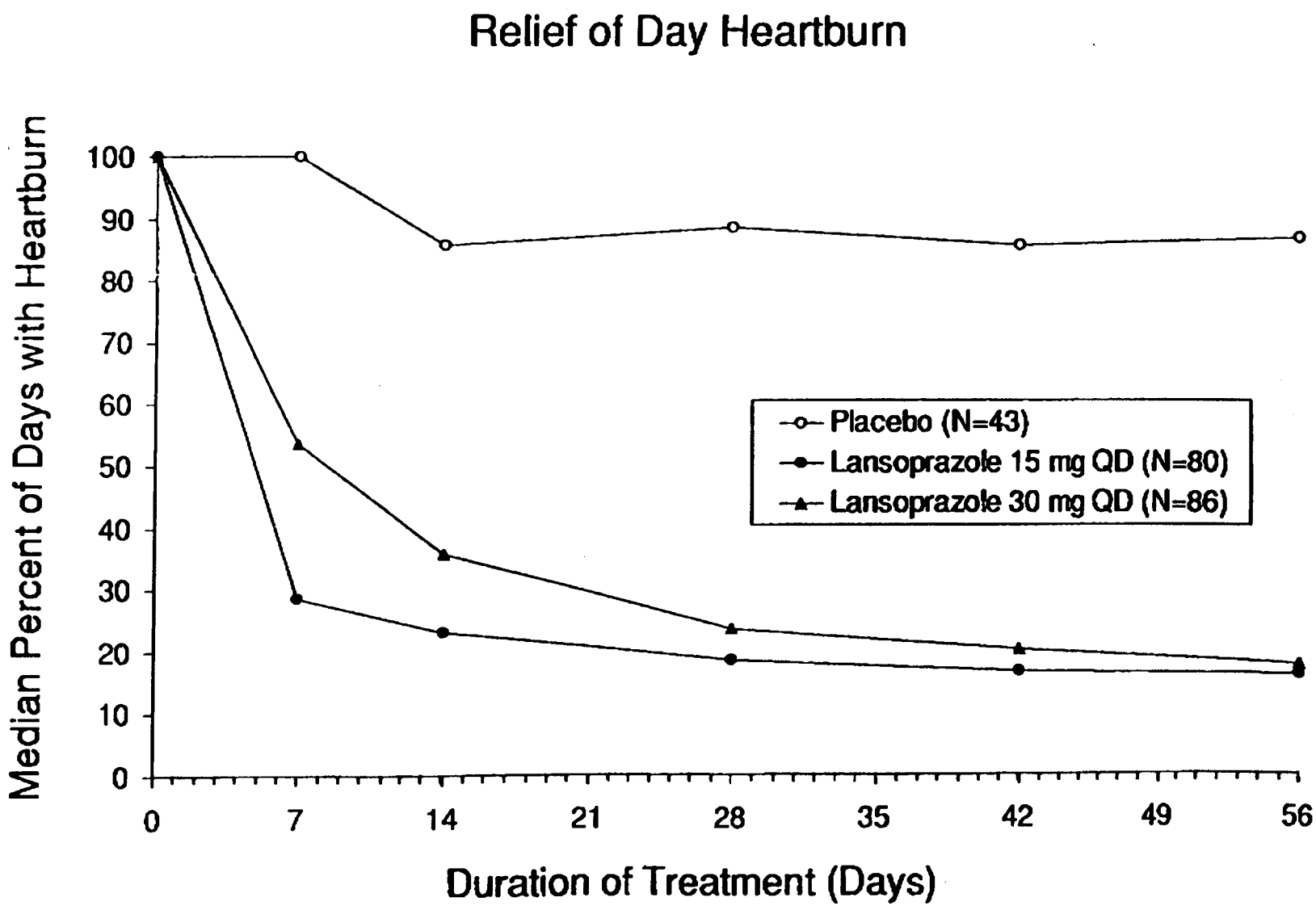
/S/ 1/7/98

Maria R. Walsh, M.S., Project Manager

cc:
Original NDA 20406/S-016
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/L.Talarico
J.Senior

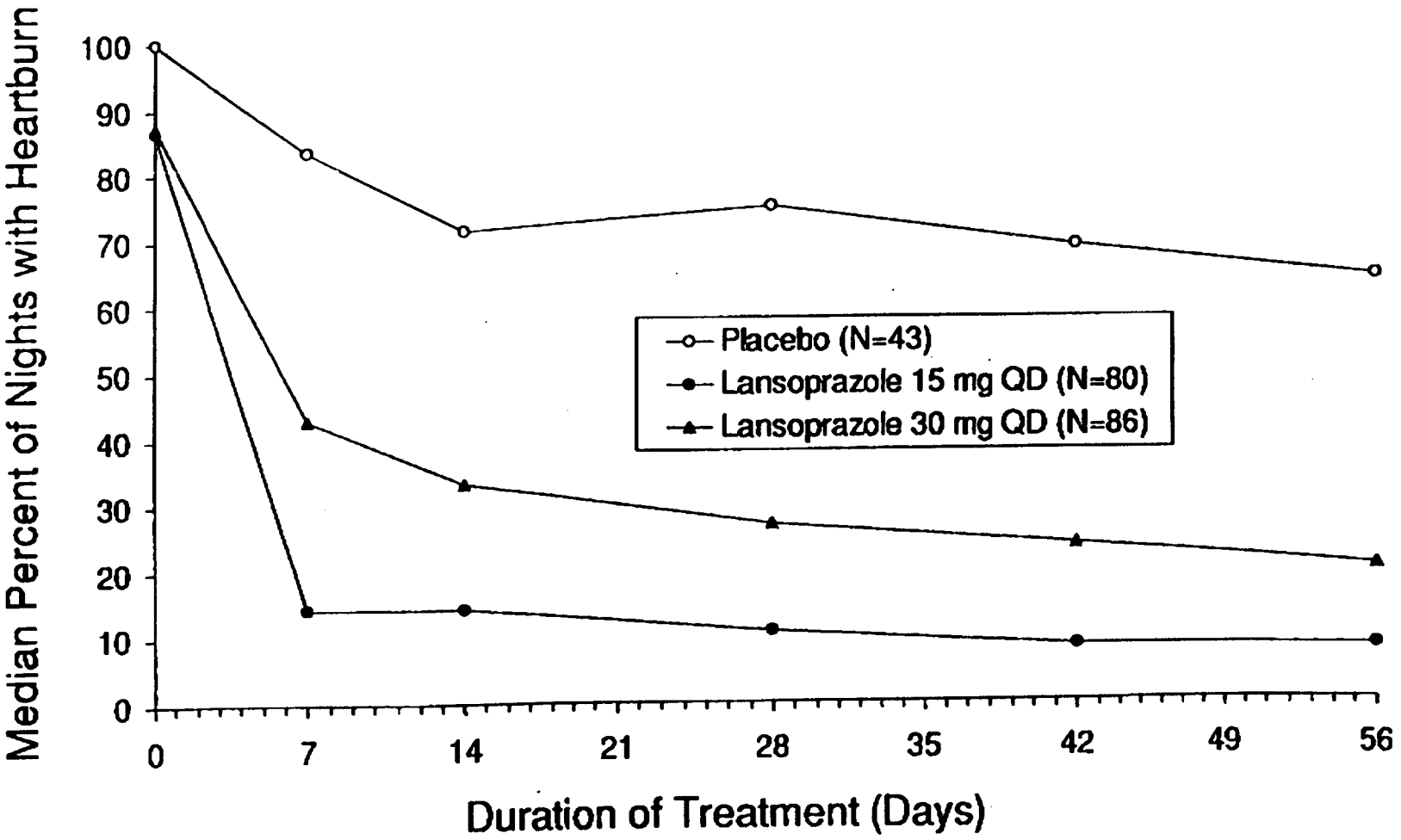
final: M.Walsh 1/7/98

CSO REVIEW



Day 0 = Median percent of day heartburn during the 7-10 days pre-treatment period

Relief of Night Heartburn



Day 0 = Median percent of night heartburn during the 7-10 days pre-treatment period

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-406/SE1-016 MAR 19 1997

Name of Drug: Prevacid (lansoprazole) Delayed-Release Capsules

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): December 20, 1996

Receipt Date(s): December 23, 1996

Background and Summary Description: NDA 20-406/SE1-016, dated December 20, 1996, provides for a new indication: short-term treatment of symptomatic gastroesophageal reflux disease (GERD).

Review

The submitted draft labeling was compared to the currently approved labeling, identified as "03-4742-R5-Rev.December, 1996" approved in supplement 012 on December 24, 1996. The following differences were noted.

1. CLINICAL STUDIES

The following subsection was added to this section:

"**Gastroesophageal Reflux Disease (GERD)**

Symptomatic GERD

In two U.S. multicenter, double-blind, placebo-controlled studies, 320 patients with endoscopically proven non-erosive GERD received therapy with lansoprazole 15 mg, 30 mg, 60 mg or placebo. Patients treated with lansoprazole 30 mg reported significantly greater relief of GERD symptoms, including heartburn and abdominal pain, and took fewer antacid tablets per day than the placebo group after both 4 and 8 weeks of treatment."

THIS REVISION MUST BE REVIEWED BY THE MEDICAL OFFICER.

2. INDICATIONS AND USAGE

The following subsection was added to this section:

> **"Gastroesophageal Reflux Disease (GERD)**
> *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."

THIS REVISION MUST BE REVIEWED BY THE MEDICAL OFFICER.

3. ADVERSE REACTIONS, Incidence in Clinical Trials

A. Special Senses

The term, "speech disorder," was added to this subsection.

B. Urogenital System

The term, "urinary retention," was added to this subsection.

THESE REVISIONS MUST BE REVIEWED BY THE MEDICAL OFFICER.

4. DOSAGE AND ADMINISTRATION

The following subsection was added to this section:

> **"Gastroesophageal Reflux Disease (GERD)**
> *Treatment of Symptomatic GERD*
> The recommended adult oral dose is 30 mg once daily for 4 to 8 weeks. (See CLINICAL STUDIES and INDICATIONS AND USAGE)."

THIS REVISION MUST BE REVIEWED BY THE MEDICAL OFFICER.

Conclusions

1. The proposed revisions to the labeling above must be reviewed by the medical officer.

2. The revisions to the package insert approved in supplement 008 (approved September 13, 1996) and supplement 012 (approved December 24, 1996) must be incorporated

into the final printed labeling (FPL) for this supplement should it be approved. Supplement 008 provides for 500, 1000, and 2500 count bottles. Supplement 012 provides for revisions to the PRECAUTIONS, Information for Patients and DOSAGE AND ADMINISTRATION sections of the package insert to include the administration of the granules through a nasogastric tube."

/S/ 3/18/97

Marla R. Walsh, Project Manager

cc:
Original NDA 20-406/S-016
HFD-180/Div. Files
HFD-180/S.Fredd
J.Senior
HFD-181/M.Walsh

3/19/97
/S/

final: M.Walsh 3/18/97

CSO REVIEW

EXCLUSIVITY SUMMARY for NDA # 20-406 SUPPL # 016

Trade Name Prevacid **Generic Name** Lansoprazole
Applicant Name Tap Holdings **HFD-** 180

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?
YES /__/ NO /✓/

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ON ORIGINAL

b) Is it an effectiveness supplement?

YES /✓/ NO /__/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

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ON ORIGINAL

d) Did the applicant request exclusivity?

YES /___/ NO /_✓_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_✓_/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_✓_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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ON ORIGINAL

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ✓ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-406 PREVACID (LANSOPRAZOLE) DELAYED-RELEASE CAPSULES

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✓/ NO /__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # M95-300

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # M95-300

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES / _ / NO / _ / Explain: _____

Investigation #2

IND # ____ YES / _ / NO / _ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / _ / Explain _____ NO / _ / Explain _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

/S/ 12/8/97

Signature Date

Title: PROJECT MANAGER

APPEARS THIS WAY
ON ORIGINAL

/S/ 3-12-98

Signature of Division Director Date

APPEARS THIS WAY

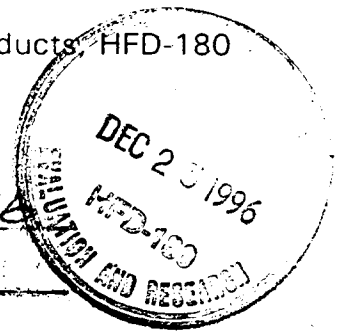
cc: Original NDA Division File HFD-85 Mary Ann Holovac

TAP HOLDINGS INC.

Lake Forest
2355 Waukegan Rd.
Deerfield, IL 60015

December 20, 1996

Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Document Control Room 6B-24
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA 20406 000
NDA SUPPL NO: SE1

Attn: Stephen B. Fredd, M.D.

RE: PREVACID® (Lansoprazole) Delayed-Release Capsules
NDA: 20-406
Supplemental Application for Labeling Change **SNDA 016**

Dear Dr. Fredd:

The sponsor, TAP Holdings Inc., submits this Supplemental Application under the provisions of Section 505 (i) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70 (b) (3).

Included in this supplement is requisite information to support a new indication for PREVACID® (lansoprazole) Delayed-Release Capsules, namely, non-erosive gastroesophageal reflux disease.

Appended is a photocopy of the cover letter and check for representing the user fee for filing a supplement with clinical data.

Finally, TAP Holdings certifies that we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application.

Please direct any questions you may have on this supplement to my attention.

Sincerely,

Judy Decker Wargel

Judy Decker Wargel
Associate Director, Regulatory Affairs
Phone: (847) 317-5781
Fax: (847) 317-5795

JDW/pjp

12/26/96

/S/

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA/PMA # 20-406 Supplement # 016 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: PREVACID (LANSOPRAZOLE) DELAYED-RELEASE CAPSULES Action: AP AE NA

Applicant TAP HOLDINGS Therapeutic Class 1S SHORT-TERM TREATMENT OF GU, DU, and EE;

Indication(s) previously approved MAINTENANCE OF HEALING OF DU and EE; PATHOLOGICAL HYPERSECRETORY CONDITIONS

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application SHORT-TERM TREATMENT OF SYMPTOMATIC GERD For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

√ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

√ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- √ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ 12/8/97

Signature of Preparer and Title Date

cc: Orig (NDA)/PLA/PMA # 20-406/S-016
HFD-180 /Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

Sponsor plans to submit

/S/
12/8/97

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

TO: File NDA 20-406/SE1-016

FROM: John R. Senior, M.D.

DATE: 8 January 1998

SUBJECT: Revised draft labeling submitted 5 January 1998

The sponsor has responded promptly to the notice that the supplemental application-016 was considered approvable on 22 December 1997, for treatment of heartburn and other symptoms associated with GERD at a daily oral dose of 15 mg of lansoprazole for up to 8 weeks. The draft labeling statements for the indication and dosing sections appear satisfactory, as provided in the Amendment No. 004, pages 016 and 023.

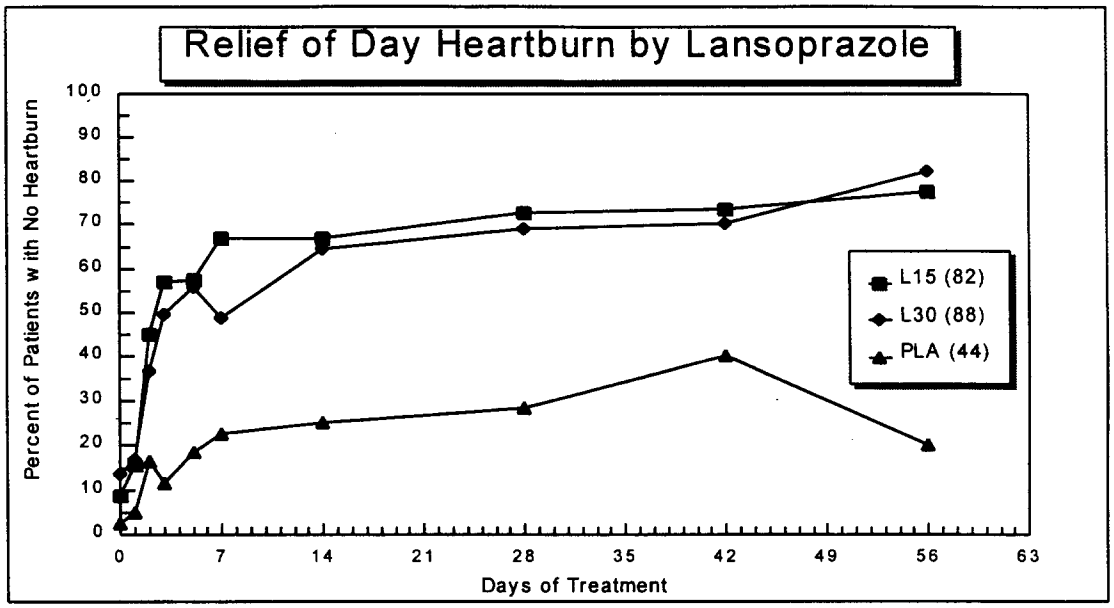
Also submitted in response to the request for a clinical data graph or table to support the new text of the Clinical Studies section are two graphs showing the median percent of days and nights with heartburn after 7, 14, 28, 42, and 56 days of treatment, and entitled "Relief of Day Heartburn" (page 011) and "Relief of Night Heartburn" (page 012). In these graphs, the pretreatment status is set at 100% based on the median percent of day or night heartburn during the 7-10 days before treatment. For these graphs, data are provided from 43 patients on placebo, 80 on lansoprazole 15 mg daily, and 86 on lansoprazole 30 mg daily. However, the text on page 010 refers to significantly greater proportions of patients reporting no day or night heartburn on both doses of lansoprazole than in those on placebo, ***after a single dose***. The graphs do not show effects on the first or second day after initiation of treatment, but give only the first data point after a week of treatment.

This creates a misleading verbal inference, not supported by the graphic data. In fact, the graphs submitted with the SE1-016 submission as Figures 8.1.1.a and 8.1.1.b on the mean severity of day and night heartburn for evaluable patients (see Volume 14, pages 066 and 067) do not support the verbal statement of such significant immediate relief after a first dose of medication. The data of those Figures and other data provided in detail in Volume 50 of the SE1-016 submission show that many patients did not respond immediately, but took a few days to show the beneficial effects of lansoprazole treatment.

In an effort to resolve this discrepancy, this reviewer has tabulated the data submitted in Volume 50 on the day-by-day diary data of heartburn severity reported by each patient in the study (except for the two patients who were randomized to lansoprazole 15 mg daily who kept no diaries, Colip #2208 and Jones #2046). The analyses of these data confirm the fact that significant response was not immediate, after a single dose, but was delayed in many patients, becoming increasingly more significant after several days and persisting with continued treatment for the 8-week period of study.

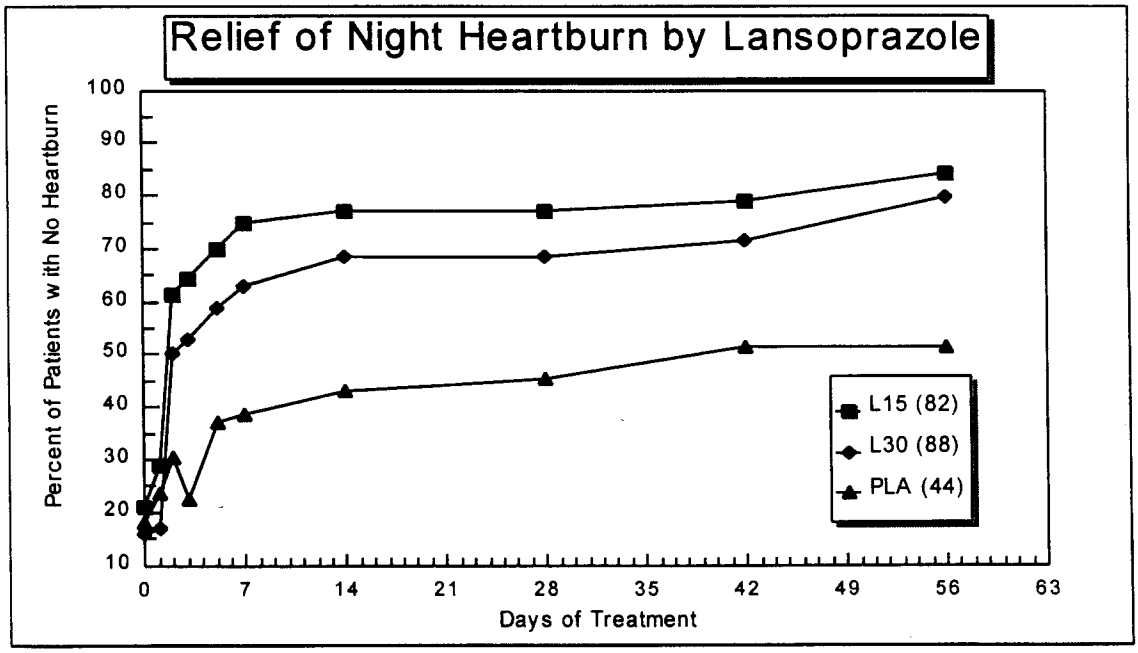
This is shown by looking at the proportions of patients who reported in their diaries no heartburn, day and night, as follows:

If we consider the proportions of patients who reported no day heartburn on Day 1 after the first dose of study medication, compared to the day before the study, it is apparent that the effects of lansoprazole are not significant yet.



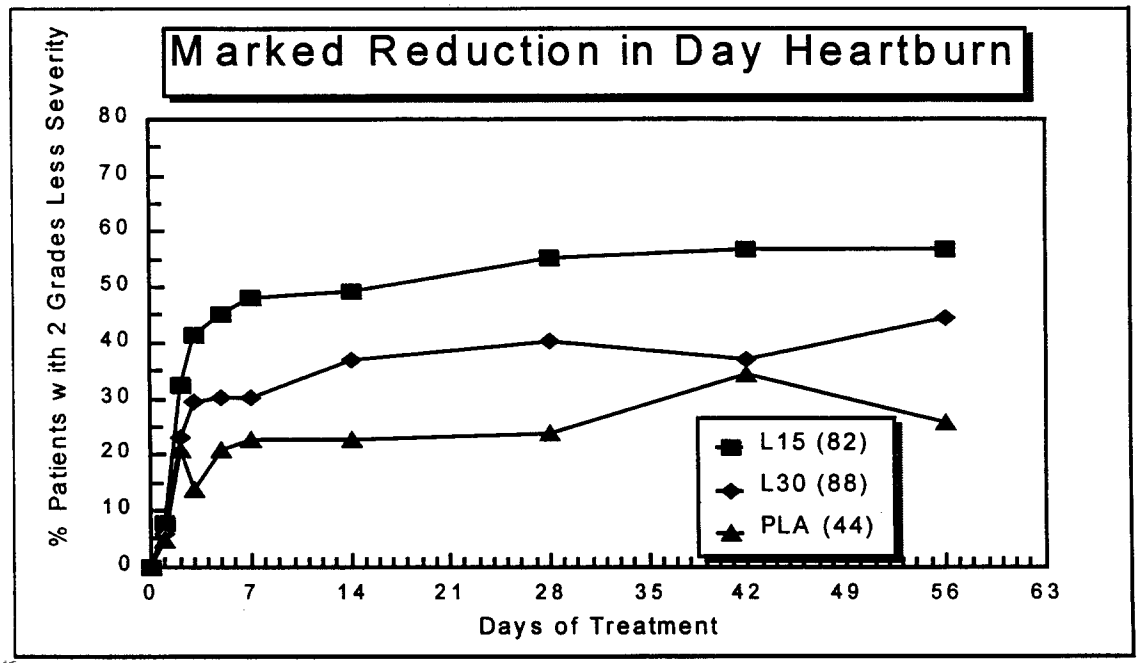
Statistical analyses of the data show lack of significant change for all three regimens:

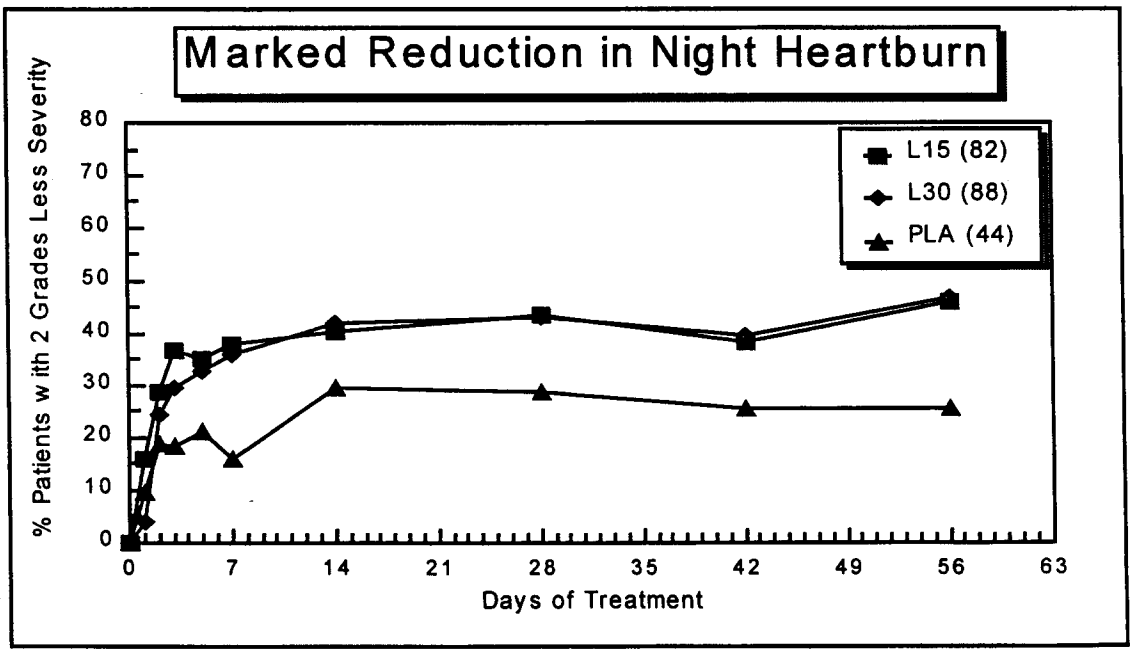
	placebo: heartburn			lanso 15: heartburn			lanso 30: heartburn		
	no	yes		no	yes		no	yes	
Day -1	1	43	44	7	73	80	12	76	88
Day 1	2	40	42	12	65	77	14	69	83
	3	83	86	19	138	157	26	145	171
$\chi 2$	0.40		p, N.S.	1.72		p, N.S.	0.35		p, N.S.



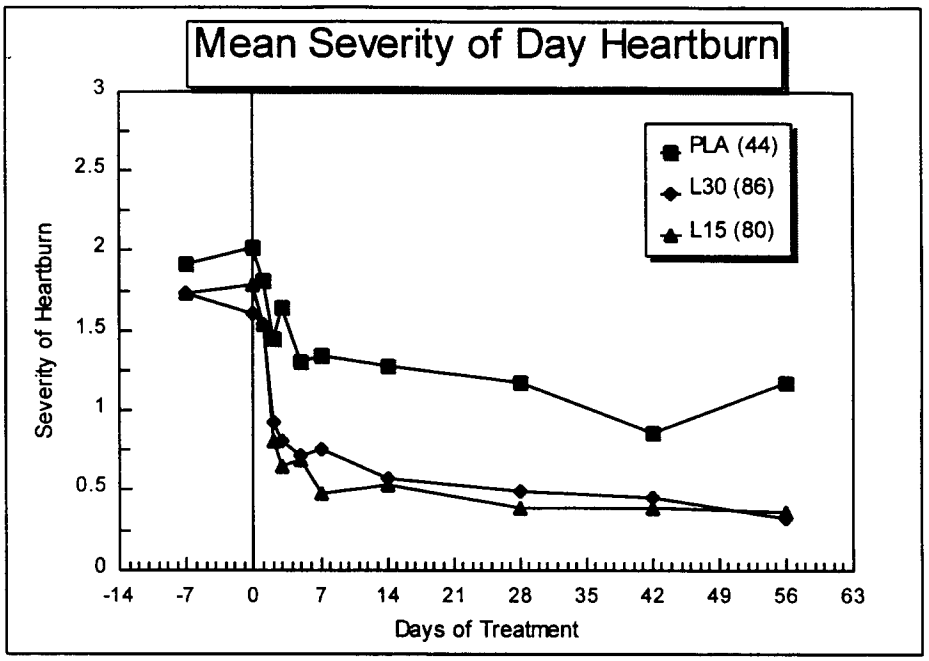
The same applies to the night heartburn, no immediate response of significantly different proportions of patients to any of the regimens, but increasingly significant responses after a few days of treatment. It is not clear where the data supporting the text statements of the draft labeling were from, because the reported percentages do not conform to the data in Volume 50. It looks as if the graphs are not taken from the same data as the text statements, which may be confusing. Better justification for the choice of which data to show must be provided, and the source of the data also. This is not to contest the results of the study, which do show lansoprazole 15 mg significantly superior to placebo, and lansoprazole 30 mg no better than lansoprazole 15 mg daily.

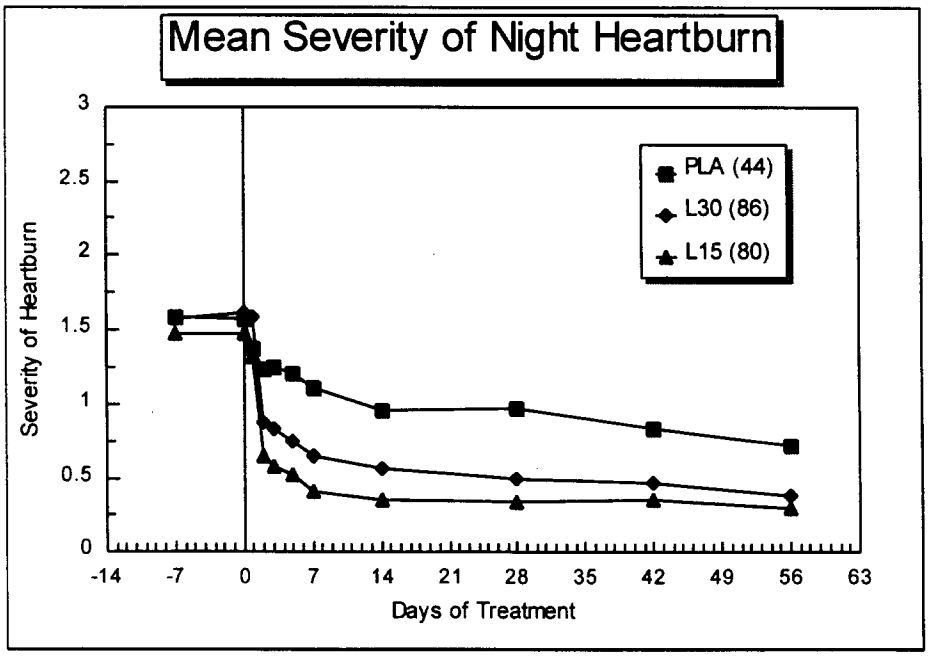
If patients reporting at least two grades of reduction in severity (from moderate to none and severe to mild or none) are considered, similar findings are obtained:



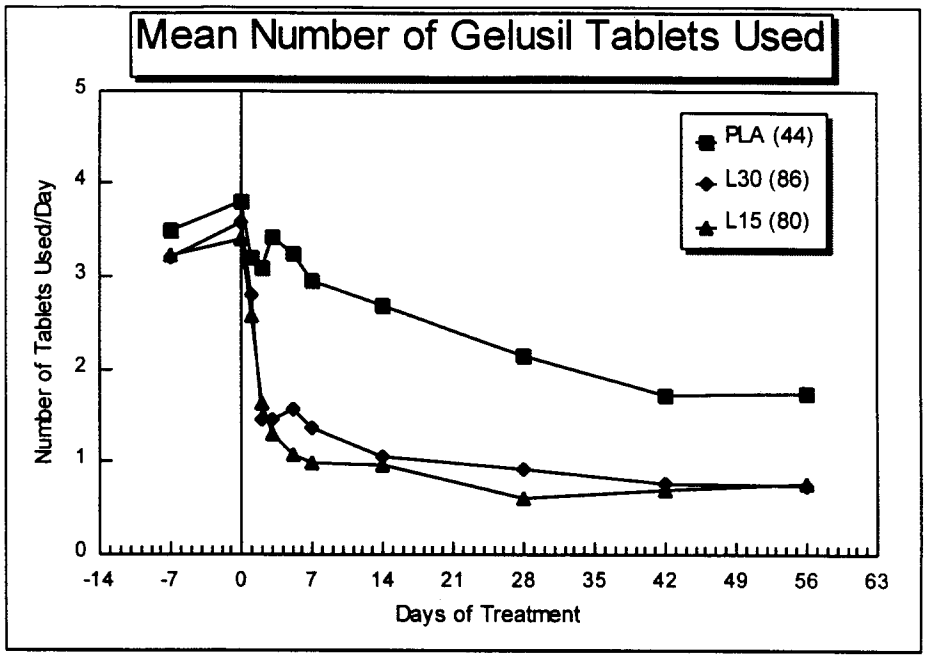


In partial replication of the sponsor's Figures 8.1.1.a and 8.1.1.b, simplified to show the mean of 7 to 14 days pretreatment median values (as -7), the means of values on pretreatment Day -1 (as 0), and then the on-treatment Days 1, 2, 3, 5, 7, 14, 28, 42, and 56, for both day heartburn and night heartburn (data taken from Volume 50 of the submission):





. . and for use of "rescue" Gelusil tablets for relief of symptoms, (next page),



It may be easily noted by inspection, and scarcely requires numerical statistical analyses, that the clearly beneficial effects of lansoprazole, especially at the 15 mg daily dose, are not seen on Day 1 after the first dose of study medication, but then become notable on the 2nd and 3rd days, then even more definite after 5 and 7 days, and thereafter. While both doses of lansoprazole are significantly superior to placebo in reducing symptoms, the 30 mg dose has no advantage over 15 mg/day.

It is suggested that the sponsor reconsider exactly which data are to be used to support both the text and graphic display of the results of Study M95-300. It may be helpful to the readers of the labeling statements and graphic displays to see results for Days 1, 3, and 5 as well as those for Days 7, 14, 28, 42, and 56, to obtain a clearer picture of the expected responses of patients with heartburn to the once daily regimen of 15 mg lansoprazole. Patients should not expect to be assured of immediate relief of chronic moderate-to-severe day and night heartburn in all cases, but should know the chance of relief in a few days is better. It is recommended that the sponsor rework the Clinical Studies section of the revised labeling.

/S/

John R. Senior, M.D., Medical Officer — 8 Jan '98 (date)
Division of Gastrointestinal and Coagulation Drug Products

cc:
NDA 20-406/SE1-016
HFD-180
HFD-180/LTalarico /S/ 2-11-98
HFD-180/JSenior
HFD-181/MWalsh
HFD-181/KJohnson

APPEARS THIS WAY
ON ORIGINAL

NDA 20-406/S-016

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

JAN 21 1998

Dear Ms. Wargel:

We acknowledge receipt on January 6, 1998 of your January 5, 1998 amendment to your supplemental new drug application (NDA) for Prevacid (lansoprazole) Delayed-Release Capsules.

This amendment contains additional labeling information submitted in response to our December 22, 1997 approvable letter.

We consider this a full response to our letter and qualifies as a Class 1 resubmission under the FDA Modernization Act of 1997. Therefore, the due date is March 6, 1998.

If you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Maria R. Walsh, M.S.
Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-406/S-016
HFD-180/Div. Files
HFD-180/CSO/M.Walsh
HFD-180/J.Senior
DISTRICT OFFICE

Drafted by: M.Walsh 1/21/98
Reviewed by: K.Johnson 1/21/98
Final: M.Walsh 1/21/98

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

NDA 20-406/S-016

DEC 26 1996

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

Dear Ms. Wargel:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Prevacid (lansoprazole) Delayed-Release Capsules

NDA Number: NDA 20-406

Supplement Number: S-016

Therapeutic Classification: Standard

APPEARS THIS WAY
ON ORIGINAL

Date of Supplement: December 20, 1996

Date of Receipt: December 23, 1996

This supplement provides for a new indication: short-term treatment of symptomatic gastroesophageal reflux disease (GERD).

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 21, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products,
HFD-180
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
ON ORIGINAL

Should you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

Maria R. Walsh
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-406/S-016
HFD-180/Div. Files
HFD-180/CSO/M.Walsh /S/ 12/23/96
DISTRICT OFFICE

Final: M.Walsh 12/23/96

SUPPLEMENT ACKNOWLEDGEMENT

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: January 21, 1998

APPLICATION NUMBER: NDA 20-406/S-016; Prevacid (lansoprazole) Delayed-Release Capsules

BETWEEN:

Name: Judy Wargel, Regulatory Affairs
Bidan Huang, Ph.D., Statistics
Phone: (847) 317-5781
Representing: TAP Holdings Inc.

AND

Name: Maria Walsh, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Revised Draft Labeling

BACKGROUND: Supplement 016, submitted December 20, 1996, provides for symptomatic gastroesophageal reflux disease (GERD) as a new indication for Prevacid and was approvable on December 22, 1997 pending revised draft labeling. The sponsor submitted revised draft labeling on January 5, 1998 (received January 6, 1998). This submission was reviewed by the medical officer and a concern was raised about the efficacy data presented in the CLINICAL TRIALS section.

TODAY'S CALL: Per Dr. Talarico, I called Ms. Wargel to discuss the January 5, 1998 revised draft labeling. Ms. Wargel wished to have a statistician present for this teleconference and called me back with Dr. Huang present. I explained that under the CLINICAL TRIALS section of the revised draft labeling, text was added by the sponsor describing the efficacy results after a single dose but the accompanying graphic data do not display the results for a day one time point but rather the first time point shown is 7 days. In addition, the data provided in the original supplement (Volume 14, pages 66 and 67) do not support a significant effect after a single dose.

Dr. Huang explained that the appropriate statistic for the first day data is the median percent and a graphic timepoint for the first day would not be meaningful since it would reflect either 0 or 100%. Therefore, the text was added to the labeling to describe the first day results as the graphs would not capture this timepoint. I commented that having the text of the efficacy results differing from the graphic data could be misleading. Further discussion revealed that the first day data was not included in the original supplement.

I requested that the sponsor submit the first day data and analysis to support the revised draft labeling. Ms. Wargel agreed to submit this information as soon as possible. The call was then

concluded.

APPEARS THIS WAY
ON ORIGINAL

/S/ 1/21/98

Maria Walsh, M.S.
Project Manager

cc: Original NDA 20-406/S-016
HFD-180/Div. File
HFD-180/M.Walsh
HFD-180/L.Talarico
J.Senior
F.Harrison

filename: 20406S16.tel

TELECON

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