CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20406/S021

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: 20-406/SE2-021

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

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): July 14, 1998

Receipt Date(s): July 15, 1998

Background and Summary Description: NDA 20-406/SE2-021 provides for the addition of a 10-day dosing regimen of triple therapy (lansoprazole/clarithromycin/amoxicillin) for the eradication of *Helicobacter pylori* to reduce the risk of duodenal ulcer recurrence. A 14-day dosing regimen was approved on June 17, 1997.

The sponsor has submitted final printed labeling (FPL) in response to the May 11, 1998 approvable letter.

Review

The submitted FPL was compared to the final draft labeling submitted on June 24, 1998 and according to the telecon dated June 29, 1998. The following differences were noted.

These revisions were approved on June 23, 1998 in supplement 024 and are acceptable.

Conclusions

The FPL is acceptable and the supplement should be approved.

/S/ 7/16/98

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

cc:
Original NDA 20-406/S-021
HFD-180/Div. Files
HFD-180/PM/M.Walsh
HFD-180/Lilia Talarico, M.D.

final: M.Walsh 7/16/98
filename: 20406S21807.rev4.doc

PM REVIEW

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-406/SE2-021

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

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): May 29, 1998

Receipt Date(s): June 1, 1998

Background and Summary Description: NDA 20-406/SE2-021 provides for the addition of a 10-day dosing regimen of triple therapy (lansoprazole/clarithromycin/amoxicillin) for the eradication of *Helicobacter pylori* to reduce the risk of duodenal ulcer recurrence. A 14-day dosing regimen was approved on June 17, 1997.

The sponsor has submitted revised draft labeling following the May 11, 1998 approvable letter which requested final printed labeling with labeling revisions. Teleconferences between the sponsor and members of the Division of Special Pathogens and Immunologic Drug Products (HFD-590) were held on June 3 and 17, 1998 to discuss the sponsor's revised draft labeling.

Review

APPEARS THIS WAY
ON ORIGINAL

The submitted revised draft labeling was compared to the original draft labeling and the labeling revisions outlined in the May 11, 1998 approvable letter (attached). The following differences were noted.

2 Page(s) Redacted

DRAFT LABELING

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Conclusions

1. The sponsor should submit final draft labeling reflecting the labeling recommendations discussed at the June 3 and 17, 1998 teleconferences with the Division of Special Pathogens and Immunologic Drug Products (as noted above).

2. The final draft labeling will be reviewed and if acceptable, the sponsor will be notified to submit final printed labeling (FPL). If the FPL is acceptable, the supplement will be approved.

/S/ 7/14/98

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

APPEARS THIS WAY
ON ORIGINAL

Attachment: May 11, 1998 approvable letter

cc:
Original NDA 20-406/S-021
HFD-180/Div. Files
HFD-180/J.Senior
H.Gallo-Torres
L.Talarico
Drafted: M.Walsh 7/1/98
Initialed by: H.Gallo-Torres 7/14/98
final: M.Walsh 7/14/98
filename: 20406S021-rev2-807.doc

PM REVIEW

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

Walsh

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-406/SE2-021

MAY - 7 1998

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

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): June 25, 1997

Receipt Date(s): June 25, 1997

Background and Summary Description: NDA 20-406/SE2-021 provides for the addition of a 10-day dosing regimen of triple therapy (lansoprazole/amoxicillin/clarithromycin) for the eradication of *Helicobacter pylori* to reduce the risk of duodenal ulcer recurrence. A 14-day dosing regimen was approved on June 17, 1997.

Review

The submitted draft labeling was compared to the currently approved labeling identified as, "03-4837-R10-Rev. March, 1998" (approved March 12, 1998 in supplement 016).

1 Page(s) Redacted

DRAFT LABELING

Conclusions

1. A team meeting was convened on April 7, 1998 between members of this Division and members of the Division of Special Pathogens and Immunologic Drug Products (HFD-590) to discuss the proposed labeling. The above recommended revisions to the proposed labeling were agreed upon and will be communicated to the sponsor in an action letter.

2. The revised draft labeling/final printed labeling must contain the revisions approved in supplement 018 (approved June 23, 1997) and supplement 016 (approved March 12, 1998).

/S/ 5/7/98

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-406/S-021
HFD-180/Div. Files
HFD-180/J.Senior
H.Gallo-Torres
L. Talarico
HFD-180/M.Walsh

final: M.Walsh 5/7/98
filename: 20406S21.rev

PM REVIEW

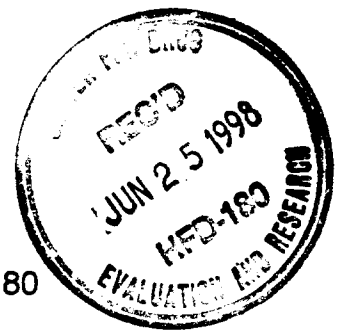
APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Lannockburn Lake Office Plaza
2355 Waukegan Rd.
Deerfield, IL 60015

June 24, 1998



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

Attn: Ms. Maria Walsh, M.S., Project Manager

RE: PREVACID® (lansoprazole) Delayed-Release Capsules

Lansoprazole with Clarithromycin and Amoxicillin for the Eradication of *H. pylori* (10-day Therapy)
NDA No. 20-406, S-021, Amendment No. 006

APPEARS THIS WAY
ON ORIGINAL

- Revised Draft Package Inset Labeling -

Dear Ms. Walsh:

The sponsor, TAP Holdings Inc. (TAP), submits this amendment to a pending Supplemental New Drug Application (SNDA) under the provisions of Section 505(I) of the Federal Food, Drug, and Cosmetic Act and 21 CFR §314.70.

The purpose of this communication is to provide the Agency with revised draft labeling for PREVACID for the indication of 10-day triple therapy (lansoprazole/amoxicillin/ clarithromycin) for the eradication of *Helicobacter pylori* (*H. pylori*). Please note that the enclosed labeling incorporates comments provided in a May 12, 1998 "approvable" letter from the GI Division as well as comments provided to TAP from members of the GI Division and the Division of Special Pathogens and Immunologic Drug Products during telephone conference calls held on June 3, 1998, June 5, 1998 and June 17, 1998. All pertinent information has been shaded for ease of review in the enclosed copy of the labeling. In addition, the enclosed draft labeling contains the following other non-*H. pylori* changes:

- Pages 20 and 25 - Information has been added to the labeling to support the *in vitro* juices administration option per NDA 20-406, Supplement Number 022, incorporating the changes requested in the approvable letter dated June 4, 1998.

- Page 25 - Formatting changes (i.e. removal of bolding, italicizing, etc.) have been made per a request by the GI and Coagulation Division

- Page 26 - In the **HOW SUPPLIED** section, additional capsule imprinting information has been added (i.e. the "TAP" logo and either "PREVACID 15" or "PREVACID 30")

- Page 26 - In the **HOW SUPPLIED** section, the statement "Caution: Federal (USA) law prohibits dispensing without a prescription" has been removed and replaced with "Rx only" per the FDA Modernization Act of 1997, Sec. 126.

Finally, please note that the adverse events labeling changes that were discussed today in a telephone call between yourself and Dr. Gary C. Magistrelli, in regard to , have not been incorporated into the enclosed draft labeling. They will, however, be incorporated into the final printed labeling.

We kindly ask for the Agency's expedited review of the proposed labeling changes before final copies of the labeling are printed. Upon concurrence from the Agency for the proposed labeling changes,

Please note that three desk copies of this submission have also been provided to the Division of Special Pathogens and Immunologic Drug Products for co-review.

Please do not hesitate to contact me if you have any questions regarding this submission.

Sincerely,

Linda J. Peters

APPEARS THIS WAY
ON ORIGINAL

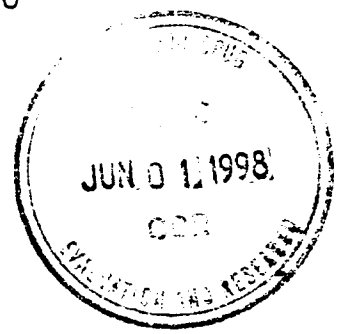
Linda J. Peters, M.S.
Manager, Regulatory Affairs
(847) 317-5481
(847) 317-5795 (fax)

LJP ljp c:\@work\word_doc\lanso\h-pyloir\amend006
attachments

CC: Ms. Robin Anderson, Project Mgr., Division of Special Pathogens and Immunologic Drug Products (HFD-590)

Dr. Bob Hopkins, Medical Officer, Division of Special Pathogens and Immunologic Drug Products (HFD-590)

TAP HOLDINGS INC.



May 29, 1998

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

Attn: Ms. Maria Walsh, M.S., Project Manager

RE: PREVACID® (lansoprazole) Delayed Release Capsules

Lansoprazole with Clarithromycin and Amoxicillin for the Eradication of *H. pylori* (10-day Therapy)
NDA No. 20-406, S-021, Amendment No. 005

- Draft Package Inset Labeling-

APPEARS THIS WAY ON ORIGINAL

Dear Ms. Walsh:

The sponsor, TAP Holdings Inc. (TAP), submits this amendment to a pending Supplemental New Drug Application (SNDA) under the provisions of Section 505(l) of the Federal Food, Drug, and Cosmetic Act and 21 CFR §314.70.

The purpose of this communication is to respond to the Agency's May 12, 1998 approvable letter for PREVACID 10-day triple therapy for the eradication of *Helicobacter pylori* (*H. pylori*). The Agency has scheduled a conference call with TAP on June 3, 1998, at 9:00 a.m., Eastern Time, to discuss the Agency's and TAP's proposed labeling changes. Therefore, included in this submission is a copy of the draft PREVACID package insert labeling for 10-day *H. pylori* therapy. Please note that the enclosed copy of the labeling incorporates the Agency's proposed changes. Also included in the draft labeling are TAP's additional proposed changes based on the Agency's May 12th comments (shown in strike-throughs for deleted wording and underlining for newly added wording).

In addition, TAP has also made one change to an incorrect study number on page 11. Study number M95-125 was incorrect and has been changed to Study No. M93-125.

Finally, per a phone call from Ms. Walsh on March 12, 1998 regarding the PREVACID Nonerosive GERD SNDA (S-016), the additional following changes were requested to be made to the labeling at the next printing:

Under **INDICATIONS AND USAGE** is the heading **Gastroesophageal Reflux Disease (GERD)** followed by *Short-Term Treatment of Symptomatic GERD.* The next heading is **Short-Term Treatment of Erosive Esophagitis.** Per Ms. Walsh's request, this heading was unbolded and italicized so it becomes a subheading under **Gastroesophageal Reflux Disease (GERD).** Ms. Walsh also requested the same formatting changes under **DOSAGE AND ADMINISTRATION**; however, we inadvertently did not make the change from bolded to italics. This will be done either in the next draft or in the final printed labeling if another draft is not required. We seek clarification from the Agency on the use of "short-term" under **INDICATIONS AND USAGE**. The subheadings under **Gastroesophageal Reflux Disease (GERD)** are *Short-Term Treatment of Symptomatic GERD* and *Short-Term Treatment of Erosive Esophagitis*. However, under **DOSAGE AND ADMINISTRATION**, the subheadings under **Gastroesophageal Reflux Disease (GERD)** are *Treatment of Symptomatic GERD* and *Treatment of Erosive Esophagitis.* Does the Agency want these changed to Short-Term Treatment of ... to be consistent with the **INDICATIONS AND USAGE** Section?

We look forward to discussing the enclosed proposed labeling changes for 10-day H. pylori therapy with the Agency on June 3rd. Please do not hesitate to contact me if you have any questions regarding this submission.

Sincerely,

Linda J. Peters

APPEARS THIS WAY
ON ORIGINAL

Linda J. Peters, M.S.
Manager, Regulatory Affairs
(847) 317-5481
(847) 317-5795 (fax)

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	05/10/09	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
5,433,959	09/03/08	Stabilized pharmaceutical composition

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EXCLUSIVITY SUMMARY for NDA # 20-406 SUPPL # 021

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 /✓/

   APPEARS THIS WAY
   ON ORIGINAL

   b) Is it an effectiveness supplement?

   YES /✓/ NO /___/

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

   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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Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

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 /✓/

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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 /___/

APPEARS THIS WAY ON ORIGINAL

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 # M95-399

Investigation #2, Study # _____

Investigation #3, Study # _____

APPEARS THIS WAY
ON ORIGINAL

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 # _____

APPEARS THIS WAY
ON ORIGINAL

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 # M95-399

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/ 7/2/98

Signature Date

Title: PROJECT MANAGER

APPEARS THIS WAY
ON ORIGINAL

/S/ 7-16-98

Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

MEMORANDUM OF TELECON

DATE: June 29, 1998

APPLICATION NUMBER: NDA 20-406/S-021; Prevacid (lansoprazole) Delayed-Release Capsules

BETWEEN:

Name: Linda Peters, M.S., Regulatory Affairs
Phone: (847) 374-5481
Representing: TAP Holdings, Inc.

AND

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

SUBJECT: Final Draft Labeling dated June 24, 1998

BACKGROUND: The sponsor submitted final draft labeling dated June 24, 1998, following discussions with the Division of Special Pathogens and Immunologic Drug Products (HFD-590) via teleconference on June 3 and June 17, 1998. Dr. Linda Utrup, microbiology reviewer, provided two comments to me via e-mail, dated June 26, 1998 (see attached), to be communicated to the sponsor.

TODAY'S CALL: I called Ms. Peters and conveyed that the final draft labeling was acceptable with the following two minor recommendations.

1. Under CLINICAL PHARMACOLOGY, MICROBIOLOGY, Helicobacter, Pretreatment Resistance: In the first sentence of this subsection, the clarithromycin pretreatment resistance test result should be 9.5% rather than 9.4%.

2. Under CLINICAL PHARMACOLOGY, MICROBIOLOGY, Helicobacter, Suspceptibility test for *Helicobacter pylori:* In the first table of this subsection, the "b" superscript in the "Amoxicillin MIC" heading should be italicized and should match the font of the preceeding "a" superscript.

Ms. Peters agreed to these recommendations and said the final printed labeling will incorporate them. The call was then concluded.

/S/ 7/10/98
Maria R. Walsh, M.S.
Regulatory Project Manager

Attachment: E-mail dated June 26, 1998

cc: Original NDA 20-406/S-021
HFD-180/Div. File
HFD-180/PM/M.Walsh
HFD-180/L.Talarico

Final: M.Walsh 7/16/98
Filename: 20406S21.tel

TELECON

APPEARS THIS WAY
ON ORIGINAL

NDA 20-406/S-021

JUL 24 1997

TAP Holdings Inc.
Attention: Linda J. Peters
2355 Waukegan Road
Deerfield, IL 60015

Dear Ms. Peters:

Please refer to your pending June 25, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid (lansoprazole) Delayed-Release Capsules.

To complete our review of the microbiology section of your submission, we request the following:

1. Both the agar dilution and E-test methodologies were used to obtain MIC results in Study M95-399. However, all of the analyses submitted utilized the MIC results obtained using the E-test methodology. Please reanalyze and resubmit all of the microbiology/resistance portions of the application using the MICs obtained by the agar dilution methodology.

2. If there are two results for a particular visit (i.e. one from the antrum, one from the corpus), the higher agar dilution MIC value should be used in the analysis.

3. Please include clinical/bacteriological outcome in Table 9.

4. Please clarify whether ampicillin was used instead of amoxicillin in both the E-test and agar dilution testing.

5. Please indicate what percentage of the isolates that were culture positive did not have agar dilution and/or E-test results.

6. Although metronidazole was not included in the therapeutic regimen, please submit the pretreatment and post-treatment agar dilution and E-test metronidazole MIC results collected during the clinical trial.

7. The adjusted E-test MIC results as listed in Table 9 should be reported as the next higher MIC value. Please refer to the following chart for this conversion:

E-test MIC	Adjusted E-test MIC
≤ 0.016	≤ 0.016
0.023	0.032
0.032	0.032
0.047	0.064
0.064	0.064
0.094	0.125
0.125	0.125
0.19	0.25
0.25	0.25
0.38	0.5
0.5	0.5
0.75	1
1	1
1.5	2
2	2
3	4
4	4
6	8
8	8
12	16
16	16
24	32
32	32
48	64
64	64
96	128
128	128
192	256
256	256
>256	>256

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

8. As requested at the June 17, 1997 meeting between the Agency and representatives of your firm, please submit clarithromycin agar dilution MIC values for the approximately 25 *H. pylori* isolates with clarithromycin E-test MIC values of > 0.125 and < 4.0 mcg/mL. This should include only patients on lansoprazole and clarithromycin dual therapies and lansoprazole, clarithromycin, and amoxicillin triple therapy.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

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

Sincerely yours,

/S/ 7-24-97

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

cc:
Original NDA 20-406/S-021
HFD-180/Div. Files
HFD-180/CSO/M.Walsh
HFD-180/L.Talarico
H.Gallo-Torres
J.Senior
HFD-590/M.Goldberger
R.Hopkins
L.Girardi
L.Utrup
C.Debellas
N.Silliman
L.Hubbard

Drafted by: M.Walsh 7/24/97
Initialed by: H.Gallo-Torres 7/24/97
L.Talarico 7/24/97
revised: M.Walsh 7/24/97
final: M.Walsh 7/24/97
filename: 20406S21.IR

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

Wilbert

NDA 20-406/S-021

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

JUL - 3 1997

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-021

Therapeutic Classification: Standard

APPEARS THIS WAY
ON ORIGINAL

Date of Supplement: June 25, 1997

Date of Receipt: June 26, 1997

This supplement provides for a 10-day dosing regimen for triple therapy, Prevacid in combination with clarithromycin and amoxicillin, for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease.

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 August 25, 1997 in accordance with 21 CFR 314.101(a).

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

Food and Drug Administration
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

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

cc:
Original NDA 20-406/S-021
HFD-180/Div. Files
HFD-180/CSO/M.Walsh /S/ 7/1/97
HFD-180/H.Gallo-Torres
J.Senior
DISTRICT OFFICE

APPEARS THIS WAY
ON ORIGINAL

Final: M.Walsh 7/1/97
filename: 20406S21.ack

SUPPLEMENT ACKNOWLEDGEMENT (AC)

CSO
Walsh

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4 February 1998

FROM: John R. Senior, M.D., Medical Officer, HFD-180
Division of Gastrointestinal and Coagulation Drug Products

SUBJECT: Concurrence with Consulting Review from HFD-590 on NDA 20-406/S-021

TO: Director, Division of Gastrointestinal and Coagulation Drug Products

---

A. Background

Division HFD-180 received in mid-January an HFD-590 medical-statistical review of the data submitted by TAP Holdings for S-021 (to show that 10 days of lansoprazole, amoxicillin, and clarithromycin was about equivalent to 14 days of treatment). The supplemental submission was received 26 June, was completed and then revised by 9 December 1997.

APPEARS THIS WAY
ON ORIGINAL

B. Comments on the Consulting Review

The data of Study M95-399 show very little if any additional benefit on Helicobacter pylori (Hp) eradication by prolonging treatment to 14 instead of 10 days of oral b.i.d. dosing with lansoprazole 30 mg, amoxicillin 1000 mg, and clarithromycin 500 mg. A total of 45 investigators enrolled 284 patients into the study, 136 to 14-day and 148 to 10-day treatment. It was a weakness of the study that 22 patients were entered who proved not to be infected with Hp by the established criteria (13 from the 10-day arm, 9 from the 14-day arm, and that another patient in the 14-day arm did not have any evidence of a duodenal ulcer (they should not have been randomized). This left 135 patients in the 10-day arm and 126 in the 14-day arm for the "modified intent-to treat" (MITT) analyses. Another 12 from the 10-day and 13 from the 14-day group were not considered "evaluable" by the sponsor, for a variety of protocol violations.

Despite these losses, there was very little difference between the two regimens and between to MITT and evaluable groups. The difference between the regimens were tiny, within about 1%, and the 95% confidence intervals were about +/- 9%. Eliminating the "non-evaluable" patients caused a slight apparent improvement of in the eradication rate, but the difference between regimens was still only 1%. The MITT rate of eradication was about 82% (72-91%, 95% C.I.).

There were no statistically significant differences in the demographic characteristics between the study groups, even when 138 patients from other studies of 14-day treatment (64 patients from M93-131 and 74 patients from M95-392) were added into the 14-day group for analyses. However, a paradoxically greater incidence of treatment-emergent adverse events was seen in the patients treated

for only 10 days (72/148, 49%) instead of for 14 days (107/274, 39%). When the "extra" 138 patients were removed (in whom the incidence of treatment-emergent adverse events was much lower, only 31% and 34%, compared to 46% in M95-399), there were no significant differences in adverse event rates between the 10- and 14-day groups of this study. The most common adverse event was diarrhea in 21 - 25% of the patients.

The medical reviewer has proposed five changes to the labeling statements, and has provided good rationale for them. The review overall is clear and concise, and I concur with the findings of the reviewers, Drs. Luigi Girardi and Nancy Silliman.

APPEARS THIS WAY
ON ORIGINAL

C. Recommendations

The review of this supplemental application by the HFD-590 reviewers is well done, and I concur with their conclusions and labeling recommendations.

APPEARS THIS WAY
ON ORIGINAL

/S/

John R. Senior, M.D. HFD-180

4 Feb 98
date

cc:
NDA 20-406, S-021
HFD-180
HFD-180/LTalarico /S/ 2-8-98
HFD-180/JSenior
HFD-180/JChoudary
HFD-180/JGibbs
HFD-180/FHarrison
HFD-181/CSO
MED/N/20406802.0JS

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

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.

(NDA)/PLA/PMA # 20-406 Supplement # 021 Circle one: SE1 (SE2) SE3 SE4 SE5 SE6
PREVACID (LANSOPRAZOLE)

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

Applicant TAP HOLDINGS Therapeutic Class IS
SHORT-TERM TREATMENT OF GU, DU, and GERD (EE + SYMPTOMATIC);

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

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

Proposed indication in this application ADDS NEW DOSING REGIMEN FOR TRIPLE THERAPY FOR H. PYLORI ERADICATION

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓ Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) ___ Infants (1month-2yrs) ✓ Children (2-12yrs) ✓ Adolescents (12-16yrs)

APPEARS THIS WAY ON ORIGINAL

___ 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. **PEDIATRIC LABELING MAY NOT BE ADEQUATE.**

- ___ a. Pediatric studies are needed.
- ___ b. Pediatric studies may not be needed but a pediatric supplement is needed.

___ 6. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓ No

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

APPEARS THIS WAY ON ORIGINAL

/S/ 7/16/98

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-406/S-021
HFD-180 /Div File
NDA/PLA Action Package
HFD-006/ KRoberts (include labeling for all NME approvals; either draft or final)

(revised 9/15/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)