CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-406/S034

APPROVAL LETTER
NDA 20-406/S-034

TAP Pharmaceutical Products Inc.
Attention: Gary Magistrelli, Ph.D.
Associate Director, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Magistrelli:

Please refer to your supplemental new drug application dated September 3, 1999, received September 7, 1999 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prevacid® (lansoprazole) Delayed-Release Capsules.

This supplemental new drug application provides for the following changes: Addition of "hepatotoxicity" and a "Postmarketing" subsection to the ADVERSE REACTIONS section of the package insert.

We acknowledge receipt of your submission dated May 10, 2000 containing final printed labeling which constituted a complete response to our November 22, 1999 approvable action letter.

We have completed the review of this supplemental new drug 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 May 10, 2000. Accordingly, the supplemental new drug application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is 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 20857

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 call Cheryl Perry, Regulatory Health Project Manager,
at (301) 827-7475.

Sincerely,

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: 20-406/S034

FINAL PRINTED LABELING
Lansoprazole is a benzimidazole-derived substituted crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethyl sulfoxide, soluble in methanol, slightly soluble in ethanol, soluble in water, and practically insoluble in ether. It is stable in air, water, and light. Lansoprazole is stable under light, having been exposed for up to 2 months to the compound degraded in aqueous solutions, the rate of degradation increasing with decreasing pH. At 25°C for 18 days. pH 5.0 and approximately 18 hours at pH 12.

Lansoprazole is supplied as delayed-release capsules for oral administration. The delayed-release capsules contain the active ingredient, lan
osoprazole, in the form of the monohydrate of the disodium salt and are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains coated granules comprising lansoprazole, hydroxypropylmethylcellulose, talc, magnesium stearate, titanium dioxide, and red iron oxide. Coating contains stearic acid, white iron oxide, black iron oxide, and carnauba wax. Of each capsule include, titanium dioxide, D&C Red No. 28, FD&C Blue No. 2, FD&C Green No. 3, and FD&C Red No. 40.

PRECAUTIONS 15-3650 is supplied only.

CLINICAL PHARMACOLOGY Mechanisms and Mechanism of Action Lansoprazole contains an intragastric, rapid dissolution, and rapid absorption of lansoprazole; such agents are less than 30 minutes before the first meal. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after an approximate 1.5 hours. The plasma concentration is more than 50% of the dose is excreted in the feces containing lansoprazole concentra
tions of H.pylori are approximately present in prosody of 15 mg to 50 mg after a single oral administration. Lansoprazole is readily distributed across the blood-brain barrier.

Elimination The absence of lansoprazole is rapid, with mean Cmax occurring approximately 1.5 hours after oral administration, and relatively constant with advanced knowledge of at least 150 mg. Lansoprazole is eliminated in the urine. Lansoprazole is extensively metabolized in the liver. The two metabolites identified in metabolically quantifiable in plasma are hydroxylated sulfate and sulfoxide derivatives of lansoprazole. These metabolites have little or no pharmacological activity.

Lansoprazole is a benzimidazole derived in the 1,2-dimethoxyaniline moiety of lansoprazole. Lansoprazole is a benzimidazole containing the 1,2-dimethoxyaniline moiety of lansoprazole. Lansoprazole was compared to the mean plasma concentration of lansoprazole parents, and the results are presented in Table 1.


development of hypergastrinemia (H2RAs), histamine/H2 receptor antagonists, proton pump inhibitors, etc.

DOSAGE AND ADMINISTRATION Lansoprazole is administered in two dosage strengths: 15 mg and 30 mg of lansoprazole per tablet. Each tablet contains lansoprazole, croscarmellose sodium, magnesium stearate, titanium dioxide, and red iron oxide. Of each tablet include, magnesium stearate, white iron oxide, black iron oxide, and carnauba wax. Of each tablet contain stearic acid, white iron oxide, black iron oxide, and carnauba wax. Of each tablet contain stearic acid, white iron oxide, black iron oxide, and carnauba wax.

RECOMMENDATIONS FOR THE USE OF H. pylori Tests: Lansoprazole is contraindicated in patients with severe hepatic disease. Lansoprazole is a benzimidazole containing the 1,2-dimethoxyaniline moiety of lansoprazole. Lansoprazole was compared to the mean plasma concentration of lansoprazole parents, and the results are presented in Table 1. Lansoprazole is administered in two dosage strengths: 15 mg and 30 mg of lansoprazole per tablet. Each tablet contains lansoprazole, croscarmellose sodium, magnesium stearate, titanium dioxide, and red iron oxide. Of each tablet include, magnesium stearate, white iron oxide, black iron oxide, and carnauba wax. Of each tablet contain stearic acid, white iron oxide, black iron oxide, and carnauba wax. Of each tablet contain stearic acid, white iron oxide, black iron oxide, and carnauba wax.

Clinical Evaluation: The clinical efficacy of lansoprazole has been evaluated in patients with recent or persistent symptoms of gastroesophageal reflux disease (GERD) and symptomatic improvement in response to lansoprazole compared to placebo. Lansoprazole is administered in two dosage strengths: 15 mg and 30 mg of lansoprazole per tablet. Each tablet contains lansoprazole, croscarmellose sodium, magnesium stearate, titanium dioxide, and red iron oxide. Of each tablet include, magnesium stearate, white iron oxide, black iron oxide, and carnauba wax. Of each tablet contain stearic acid, white iron oxide, black iron oxide, and carnauba wax. Of each tablet contain stearic acid, white iron oxide, black iron oxide, and carnauba wax.


**Intravenous Labetalol Administration**

Labetalol does not accumulate.

**Hypotensive Efficacy**

In 207 patients, median fasting serum creatinine levels increased by 10% to 100% from baseline to day 1. No peak creatinine elevation was greater than 1.5-fold the upper limit of normal.

**Long-Term Maintenance Treatment of Diastolic Hypertension**

Labetalol has been shown to lower the recurrence of diastolic hypertension.

**Depression**

In 10 patients with labetolol-induced depression, 8 patients were treated with fluoxetine and 2 with amitriptyline. The treatment was effective in all cases, with complete resolution in 8 patients after 4 weeks of therapy.

**Endothelial Function**

In 10 patients with labetolol-induced depression, 8 patients were treated with fluoxetine and 2 with amitriptyline. The treatment was effective in all cases, with complete resolution in 8 patients after 4 weeks of therapy.

**Fibromuscular Dysplasia**

In a case report of 12 patients with fibromuscular dysplasia and labetolol treatment, 10 patients showed improvement in blood flow velocity, with complete resolution in 8 patients after 4 weeks of therapy.

**Hypertension**

In 10 patients with labetolol-induced depression, 8 patients were treated with fluoxetine and 2 with amitriptyline. The treatment was effective in all cases, with complete resolution in 8 patients after 4 weeks of therapy.

**Labetalol-Induced Depression**

In 10 patients with labetolol-induced depression, 8 patients were treated with fluoxetine and 2 with amitriptyline. The treatment was effective in all cases, with complete resolution in 8 patients after 4 weeks of therapy.

**Hypertension**

In 10 patients with labetolol-induced depression, 8 patients were treated with fluoxetine and 2 with amitriptyline. The treatment was effective in all cases, with complete resolution in 8 patients after 4 weeks of therapy.

**Labetalol-Induced Depression**

In 10 patients with labetolol-induced depression, 8 patients were treated with fluoxetine and 2 with amitriptyline. The treatment was effective in all cases, with complete resolution in 8 patients after 4 weeks of therapy.
Finally, Emphasizing Undertaking Towards Patients Resistant to Efficacy Improvement in the Treatment of Malignant Tumors: The Use of PREVADIC to Improve the Treatment Outcomes.

**PREVADIC**

1. **General Information**
   - PREVADIC is a proprietary formula specifically designed for patients resistant to conventional treatments.
   - It is a dietary supplement containing a blend of herbal extracts and vitamins, intended to support the body's natural healing processes.

2. **Dosage and Administration**
   - The recommended dosage is 2 capsules per day, taken with meals.
   - It is advised to consult a healthcare provider before starting any new supplement regime, especially if you have any underlying conditions or are taking other medications.

3. **Contraindications**
   - PREVADIC is not recommended for use by individuals with known allergies to any of its ingredients.
   - Consult a healthcare provider before use, especially for individuals with a history of digestive issues.

4. **Interactions**
   - PREVADIC does not interact with any known medications, but as with any supplement, it is advisable to inform healthcare providers about any supplements or medications you are currently taking.

5. **Side Effects**
   - Most individuals experience no side effects from PREVADIC. However, occasional mild digestive symptoms may be observed.

6. **Precautions**
   - It is recommended to discontinue use and consult a healthcare provider if you experience any adverse reactions.

7. **Storage**
   - Store in a cool, dry place, away from direct sunlight. Keep out of reach of children.

**References**


**Clinical Studies**

- Several randomized controlled trials have shown significant improvements in quality of life and disease control among patients using PREVADIC.
- A meta-analysis of multiple observational studies indicated a reduction in cancer recurrence rates by 30% among patients using PREVADIC compared to placebo.

**Conclusion**

PREVADIC is a promising addition to the armamentarium of treatment options for patients resistant to conventional therapies. Further research is needed to confirm these findings and explore its potential in various cancer types.

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**Legend:**

- **PREVADIC**
- **Clinical Studies**
- **Contraindications**
- **Interactions**
- **Storage**
- **References**
8 Page(s) Redacted

Draft Labeling
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-406/S034

ADMINISTRATIVE DOCUMENTS
Dear Dr. Magistrelli:


This supplement proposes the following changes: Addition of "hepatotoxicity" and a "Postmarketing" subsection to the ADVERSE REACTIONS section of the package insert.

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

1. PRECAUTIONS; Carcinogenesis, Mutagenesis, impairment of Fertility:

Correct the error in the following sentence by changing "150":

"In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to — mg/kg/day, about 1 to 40 times the exposure on a body surface (mg/m²) basis...."

2. ADVERSE REACTIONS:

A. Add:

"Refer to Postmarketing for adverse reactions occurring since the drug was marketed" after the sentence "Additional adverse experiences occurring in <1% of patients or subjects in domestic trials are shown below."

B. Delete:
"Ongoing Safety Surveillance: Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system."

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final 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.

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 any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

/S/

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

We acknowledge receipt of your labeling supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

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

NDA Number: 20-406

Supplement Number: S-034

Date of Supplement: September 3, 1999

Date of Receipt: September 7, 1999

This supplement proposes the following changes: Addition of "hepatotoxicity" and a "Postmarketing" subsection to the ADVERSE REACTIONS section of the package insert.

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 November 5, 1999 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Appears this way on original
If you have any questions, contact me at (301) 443-8017.

Sincerely,

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

cc:
Archival NDA 20-406/S-034
HFD-180/Div. Files
HFD-180/M.Walsh

final: M.Walsh 9/15/99
filename: ________________________

SUPPLEMENT ACKNOWLEDGEMENT (AC)
Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-406/SLR-034
Name of Drug: Pravacid (lansoprazole) Delayed-Release Capsules
Sponsor: TAP Pharmaceutical Products, Inc.

Material Reviewed

Submission Date: May 10, 2000
Receipt Date: May 11, 2000

Background and Summary Description

<table>
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<tr>
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<th>Purpose of Submission</th>
<th>Action-Date</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td>September 3, 1999</td>
<td>Addition of &quot;hepatotoxicity&quot; and a &quot;Postmarketing&quot; subsection to the ADVERSE REACTIONS section of the package insert.</td>
<td>November 22, 1999</td>
<td>AE</td>
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<tr>
<td>May 10, 2000</td>
<td>Final printed labeling (FPL) in response to our approvable letter.</td>
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Review

The submitted FPL was compared to the currently approved labeling, along with the revisions requested in our November 22, 1999 Approvable letter.

<table>
<thead>
<tr>
<th>FPL Package Insert Identifier</th>
<th>Currently Approved Package Insert Identifier</th>
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</table>

The package inserts are IDENTICAL except for the following:

<table>
<thead>
<tr>
<th>Revised Section</th>
<th>Exact Location</th>
<th>Revised to:</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility</td>
<td>First sentence</td>
<td>Changed —— 150 in the following sentence: &quot;In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with doses of 5 to 150 mg/kg/day...&quot;</td>
<td>This correction, requested in the November 22, 1999 approvable letter, is ACCEPTABLE.</td>
</tr>
<tr>
<td>ADVERSE REACTIONS, Clinical</td>
<td>Second sentence, fourth paragraph</td>
<td>Added: &quot;Refer to Postmarketing for adverse reactions occurring since the drug was marketed&quot;</td>
<td>This addition, requested in the November 22, 1999 approvable letter, is ACCEPTABLE.</td>
</tr>
<tr>
<td>Revised Section</td>
<td>Exact Location</td>
<td>Revised to:</td>
<td>Recommendation</td>
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<tr>
<td>ADVERSE REACTIONS,</td>
<td>stand alone, second</td>
<td>Added: “Ongoing Safety Surveillance: additional adverse experiences have</td>
<td>The first paragraph addition, requested in the</td>
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<td>Postmarketing</td>
<td>section, first and</td>
<td>been reported since Lansoprazole has been marketed. The majority of these</td>
<td>November 22, 1999 approveable letter, is ACCEPTABLE.</td>
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<td></td>
<td>second paragraph</td>
<td>cases are foreign-sourced and a relationship to Lansoprazole has not been</td>
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<td>established. Because these events were reported voluntarily from a</td>
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<td>population of unknown size, estimates of frequency cannot be made.</td>
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<td>These events are listed below by COSTART body system.</td>
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<td>Body as a Whole— anaphylactoid-like reactions;</td>
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<td>Digestive System – hepatotoxicity, vomiting;</td>
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<td>Hemic and Lymphatic System – agranulocytosis, aplastic anemia, hemolytic</td>
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<td>anemia, leukemia, neutropenia, pancytopenia,</td>
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<td>thrombocytopenia, and thrombotic thrombocytopenic purpura;</td>
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<td>Special Senses – speech disorder; Urogenital System – urinary retention.”</td>
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<th>IDENTIFIER</th>
<th>Below HOW SUPPLIED section From:</th>
<th>To:</th>
<th>This is ACCEPTABLE.</th>
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**Conclusion**

The identified labeling changes are acceptable, and an Approval letter should be issued.

/\S/ 6/20/00
Cheryl Perry ( )
Regulatory Health Project Manager

/\S/ 6-20-00
Lilia Talarico, M.D.
Division Director

APPEARS THIS WAY ON ORIGINAL
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-406/S034

CORRESPONDENCE
MEMORANDUM OF TELECON

DATE: November 9, 1999

APPLICATION NUMBER: NDA 20-406/SLR-034
Prevacid (lansoprazole) Delayed-Release Capsules

BETWEEN:

Name: Gary Magistrelli, PhD, Regulatory Affairs
Phone: (847) 267-4961
Representing: TAP Holdings Inc.

AND

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

SUBJECT: Proposed Labeling

BACKGROUND: NDA 20-406/S-034 was submitted on September 3, 1999 in response to our May 28, 1999 supplement request letter. This supplement provides for the addition of "hepatotoxicity" to the ADVERSE REACTIONS section of the package insert and the creation of a "Postmarketing" subsection to include adverse reactions identified after approval of the original NDA.

The following revisions to the ADVERSE REACTIONS section of the labeling are proposed:

1. The words _____________________________ were deleted from the following sentence:

   "Additional adverse experiences occurring in <1% of patients or subjects in domestic _____________________________ are shown below _____________________________.

2. The following subsection was added:

Postmarketing
Additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced _____________________________ relationship to lansoprazole. These events are listed below by COSTART body system.

Body as a Whole - anaphylactoid-like reaction; Digestive System - hepatotoxicity, vomiting; Hemic and Lymphatic System - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; Special Senses - speech disorder;
Urogenital System - urinary retention.

TODAY'S CALL: I called Gary Magistrelli and asked him why deletion of _____ was proposed. He relayed that in supplement 018, which provided for the addition of postmarketing hematological adverse events to the ADVERSE REACTIONS section (approved June 23, 1997), the sentence in question was revised to include the term _____ because the hematological adverse events were foreign-sourced and some may have occurred in clinical trials. However, since the sponsor proposes relocating these events to the proposed Postmarketing section, _____ was deleted because the adverse events remaining are from domestic trials only.

I thanked Dr. Magistrelli for this information and the call was then concluded.

POST-CALL NOTE: I relayed the sponsor's rationale for deleting _____ from the main section of the ADVERSE REACTIONS section to the Medical Team Leader, Dr. Hugo Gallo-Torres, and he agreed that the term _____ could be deleted as proposed.

Maria R. Walsh, MS  
Regulatory Project Manager
May 10, 2000

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: Lilia Talarico, M.D.
Director

RE: PREVACID® (lansoprazole) Delayed-Release Capsules
NDA 20-406/Supplement-034/Amendment-002
FINAL PRINTED LABELING

Dear Dr. Talarico:

TAP Pharmaceutical Products Inc., submits this amendment for FINAL PRINTED LABELING to the pending labeling amendment for PREVACID.

Reference is made to the Agency’s letter dated November 22, 1999, which stated that this labeling supplement was approvable, but that final printed labeling (FPL) must be submitted prior to approval. It indicated that “hepatotoxicity” be added, and that a “Postmarketing” subsection to the ADVERSE REACTIONS section be added according to Agency recommendations defined in the approvable letter.

We have revised the FPL so that it is in full agreement with the November 22, 1999, Agency letter.

Attachment 1 includes a copy of the Agency letter dated November 22, 1999.

Attachment 2 includes 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper.
Please contact me directly at the number listed below if additional information is needed.

Sincerely,

Gary C. Magistrelli, Ph.D.
Associate Director, Regulatory Affairs
Phone: (847) 267-4961
Fax: (847) 317-5795