CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-406/S024

Trade Name: Prevacid Delayed Release Capsules

Generic Name: (lansoprazole)

Sponsor: TAP Holdings Inc

Approval Date: June 23, 1998
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-406/S024

APPROVAL LETTER
TAP Holdings, Inc.
Attention: Gary C. Magistrelli, Ph.D.
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Magistrelli:


The user fee goal date for this application is July 12, 1998.

This supplemental new drug application provides for the following changes to the ADVERSE REACTIONS section of the package insert: Addition of "anaphylactoid-like reaction" under the subheading, Body as a Whole, and the substitution of "blurred vision" for "amblyopia" in the subheading, Special Senses.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert dated January 7, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. In addition, all previous revisions as reflected in the most currently approved package insert must be included.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-406/S-024." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

If a letter communicating important information about this drug product (i.e., a "Dear Healthcare 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, contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely,

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

cc:
Archival NDA 20-406
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/J.Senior
HFD-180/H.Gallo-Torres
HFD-180/L.Talarcio
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

final: M.Walsh 6/23/98
filename: 20406S24-AP806.doc
DESCRIPTION

The active ingredient in PREVACID (lansoprazole) Delayed-Release Capsules is a substituted benzimidazoles, 1-[[3-(methyl-4-aryl-2,3-dihydro-1H-indazol-5-yl)-3-pyridyl] methyl] benzimidazole, a compound that inhibits gastric acid secretion. The empirical formula is C_{25}H_{21}N_{5}O_{5}. The molecular weight is 435.4.

Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide, soluble in methanol, sparingly soluble in ethanol, slightly soluble in ethyl acetate, dichloromethane and acetone, very slightly soluble in ether, and practically insoluble in hexane and water.

Lansoprazole is stable when exposed to light for up to two months. The compound degrades in aqueous solution, the rate of degradation increasing with increasing pH. At pH 2 the t1/2 is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0.

PREVACID is supplied in delayed-release capsules for oral administration. The delayed-release capsules contain the active ingredient, lansoprazole, in the form of enteric-coated granules and are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole, hydroxypropylmethylcellulose, low substituted hydroxypropylmethyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, aqueous starch, sucrose, polyethylene glycol, polyvinyl alcohol, and titanium dioxide. Coatings of the gelatin capsule include gelatin, titanium dioxide, E210 Red No. 3, FD&C Blue No. 1, FD&C Green No. 3, and FD&C Red No. 40.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

PREVACID Delayed-Release Capsules contain enteric-coated granules formulation of lansoprazole. Absorption of lansoprazole begins only after the granules reach the stomach. Absorption is rapid, with mean plasma levels of lansoprazole occurring approximately 1.7 hours after oral dosing, and relatively complete with absolute bioavailability over 80%. In healthy subjects, the t1/2 is 1.5 (±0.9) hours. Both Cmax and t1/2 are increased by about 50% if the drug is given 30 minutes after food as compared to fasting conditions. There is no significant food effect if the drug is given before meals.

Distribution

Lansoprazole is 97% bound to plasma protein. Plasma protein binding is constant over the concentration range of 0.05 to 30.0 mg/mL.

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in plasma (the hydroxy and sulfone derivatives of lansoprazole). These metabolites have very little or no antimicrobial activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by PDE-5. After oral administration, the drug is present within the parietal cell membrane, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of assumed to be the same effects for at least one year. Human studies have demonstrated that the active form of lansoprazole is not substantially excreted in urine or feces.

Clinically relevant effects:

Human studies for up to one year have not detected any clinically significant effects on the respiratory system. Lansoprazole did not induce adenocarcinoma, hamartomas, or other hyperplastic lesions in rats. Lansoprazole at the dose of 60 mg/kg/day for two to four weeks had no clinically significant effect on thyroid function. In 24-month carcinogenicity studies in Sprague-Dawley rats and B6C3F1 mice, exposure to up to 150 mg/kg/day over 100 days caused changes in the liver, including benign tumors, which were preceded by changes in control rats. Induced tumors were all benign, and no other changes were observed.

Other effects

No systemic effects of lansoprazole were observed in the greatest practicable number of animals used. The highest treatment-related effects observed in the studies were mild and did not change significantly from those observed in untreated animals. Lansoprazole was safe and well tolerated by animals over a wide range of doses. In studies in which lansoprazole was administered for up to 24 months, the lowest dose reported was 15 mg/kg/day in rats and 30 mg/kg/day in mice. In these studies, no major change in body weight, food consumption, or activity was observed.

CLINICAL PHARMACOLOGY

MICROBIOLOGY

Lansoprazole, clarithromycin, and/or amoxicillin have been shown to be active against certain strains of Helicobacter pylori in vitro and in clinical isolates as described in the INDICTIONS AND USAGE section.

Helicobacter pylori

H. pylori Eradication Rates – Triple Therapy (PREVACID (lansoprazole) delayed-release)

Percent of Patients Cured (95% Confidence Interval) (Number of patients)

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Triple Therapy</th>
<th>Triple Therapy Intent-to-Treat (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M95-131</td>
<td>14 days</td>
<td>90% (80.9-95.7) (N=108)</td>
<td>80% (73.3-86.5) (N=105)</td>
</tr>
<tr>
<td>M95-392</td>
<td>14 days</td>
<td>86% (75.7-95.5) (N=108)</td>
<td>83% (77.4-88.7) (N=106)</td>
</tr>
<tr>
<td>M95-399</td>
<td>14 days</td>
<td>85% (77.8-92.0) (N=113)</td>
<td>86% (79.6-92.1) (N=116)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Triple Therapy</th>
<th>Triple Therapy Intent-to-Treat (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M95-131</td>
<td>10 days</td>
<td>84% (76.4-88.8) (N=123)</td>
<td>83% (73.8-87.6) (N=135)</td>
</tr>
</tbody>
</table>

* Based on available patients with confirmed duodenal ulcer (active or healed) within one year and H. pylori test results defined as negative or positive results in the Logstata CR test. Additional, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the evaluation as patients who were not treated with any study drug. Additional, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the evaluation as patients who were not treated with any study drug.

H. pylori Eradication Rates – 14-Day Triple Therapy (PREVACID (lansoprazole) delayed-release)

Percent of Patients Cured (95% Confidence Interval) (Number of patients)

<table>
<thead>
<tr>
<th>Study</th>
<th>Dual Therapy</th>
<th>Dual Therapy Intent-to-Treat (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M95-131</td>
<td>77% (95.1-100) (N=111)</td>
<td>75% (94.8-96.2) (N=102)</td>
</tr>
<tr>
<td>M95-125</td>
<td>68% (95.1-100) (N=114)</td>
<td>62% (94.8-100) (N=102)</td>
</tr>
</tbody>
</table>

* Based on available patients with confirmed duodenal ulcer (active or healed) within one year and H. pylori test results defined as negative or positive results in the Logstata CR test. Additional, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the evaluation as patients who were not treated with any study drug. Additional, if patients dropped out of the study due to an adverse event related to the study drug, they were included in the evaluation as patients who were not treated with any study drug.
The acetylsalicylic effect on platelet aggregation was not investigated in patients 18 years of age, and the 12 men and 6 women had no history of cardiovascular or metabolic disease. All patients gave written informed consent to participate in the study.

Methods

The study was approved by the Institutional Review Board of the University of California, San Francisco.

Results

A total of 200 patients were included in the analysis. The mean age of the patients was 52 years, and the mean body mass index was 26 kg/m². The median dose of aspirin was 150 mg/day, and the mean dose was 250 mg/day. The median duration of follow-up was 30 months, and the mean duration was 36 months.

The primary outcome of interest was the rate of cardiovascular events, defined as a composite of myocardial infarction, stroke, and vascular death. The secondary outcomes were the rates of individual cardiovascular events, including non-fatal myocardial infarction, non-fatal stroke, and vascular death.

The primary endpoint was the time to the first cardiovascular event. The secondary endpoints were the time to the first non-fatal myocardial infarction, the time to the first non-fatal stroke, and the time to the first vascular death.

The results showed that aspirin significantly reduced the rate of cardiovascular events by 28% (95% CI 16% to 39%). The reduction was observed in both men and women, and in both smokers and non-smokers. The rate of non-fatal myocardial infarction was reduced by 24% (95% CI 10% to 38%), the rate of non-fatal stroke was reduced by 18% (95% CI 1% to 34%), and the rate of vascular death was reduced by 34% (95% CI 13% to 53%).

The incidence of gastrointestinal side effects was low, with 112 patients (56%) reporting at least one event during the study. The most common adverse events were abdominal pain, nausea, and diarrhea. There were no significant differences in the incidence of adverse events between the aspirin and placebo groups.

Conclusion

Aspirin is an effective and safe medication for reducing the risk of cardiovascular events in patients 18 years of age and older. The benefits of aspirin outweigh the risks, and it is recommended as a primary prevention strategy for patients with a 10-year atherosclerotic cardiovascular disease risk of 10% or higher.
**Pharmacodynamics**

Lacosamide belongs to a class of anticonvulsant compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H1-receptor antagonistic properties, but that may have agonistic activity and specific synaptic contact of [GABA A] receptors, which are the primary inhibitory synapses in the motor control system. The direct interaction of lacosamide with these receptors may result in suppression of neuronal activity.

**Mechanism of Action**

Lacosamide is an anticonvulsant drug that is used to treat partial onset seizures and medication-resistant epilepsy. It works by decreasing the activity of certain nerve cells in the brain.

**Pharmacokinetics**

Lacosamide is rapidly absorbed after oral administration, with peak plasma levels achieved within 1-2 hours. It is extensively metabolized in the liver and primarily excreted in the urine.

**Dosage and Administration**

The usual starting dose is 25 mg twice daily, with increments of 25 mg every 3-4 days up to a maximum daily dose of 400 mg. The dose should be reduced in patients with hepatic impairment.

**Adverse Effects**

Common adverse effects include dizziness, headache, and nausea. More severe side effects are rare but can include agranulocytosis and bone marrow suppression.

**Interactions**

Lacosamide affects the metabolism of many other drugs, so it is important to monitor for drug interactions.

**Case Study**

A 40-year-old woman with a history of seizures was started on lacosamide. She reported experiencing dizziness and headache within the first week of treatment. The dose was reduced from 100 mg twice daily to 50 mg twice daily, and her symptoms improved.

**Conclusion**

Lacosamide is an effective anti-epileptic drug with a good safety profile. However, it is important to monitor patients for side effects and drug interactions.
Interference with effect.

Laxantloose causes a profound and long-lasting inhibition of gastric acid secretion, therefore, is a very effective antacid. It is also used in patients with peptic ulcer disease and after operations for gastric surgery, as it decreases the absorption of drugs when gastric pH is in an important determinant of bioavailability (e.g., ketone bodies, ampicillin, etc.).

Endoscopic Reevaluation Rates

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>No. of Reevaluations</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>98</td>
<td>98%</td>
</tr>
<tr>
<td>150</td>
<td>149</td>
<td>99%</td>
</tr>
<tr>
<td>200</td>
<td>198</td>
<td>99%</td>
</tr>
<tr>
<td>250</td>
<td>248</td>
<td>99%</td>
</tr>
<tr>
<td>300</td>
<td>298</td>
<td>99%</td>
</tr>
<tr>
<td>350</td>
<td>348</td>
<td>99%</td>
</tr>
<tr>
<td>400</td>
<td>398</td>
<td>99%</td>
</tr>
</tbody>
</table>

**Maintenance of Treatment of Eosinophilic Esophagitis**

The recommended adult dose is 15 mg once daily for up to 8 weeks. (See CLINICAL STUDIES.)

**Gastroesophageal Reflux Disease (GERD) Short-Term Treatment of Eosinophilic Esophagitis**

The recommended adult dose is 15 mg once daily for up to 8 weeks. (See CLINICAL STUDIES.)

**Maintenance of Healing of Eosinophilic Esophagitis**

The recommended adult dose is 15 mg once daily for up to 8 weeks. (See CLINICAL STUDIES.)

**Pathological Hypersensitivity Conditions Including Zollinger-Ellison Syndrome**

The dosage of PREVACID in patients with pathological hypersensitivity conditions varies with the individual patient. The recommended adult dose is 15 mg once daily for up to 8 weeks. (See CLINICAL STUDIES.)

**HOW SUPPLIED**

PREVACID Delayed-Release Capsules are supplied as beige, oval, flat, scored, and marked with "PREVACID 15 mg" on the cap and "15 mg" on the body. They are available as 15 mg scored, orange, scored, and marked with "PREVACID 30 mg" on the cap and "30 mg" on the body. They are available as 30 mg scored, green, scored, and marked with "PREVACID 45 mg" on the cap and "45 mg" on the body.

**ADVERSE REACTIONS**

Over 60,000 patients have been treated with PREVACID in Phase 2-3 clinical trials involving various dosage and durations of treatment. In general, long-term treatment has been well tolerated in both short-term and long-term trials. The adverse effects noted during clinical studies are divided into major categories to help the physician in making the right decision to the drug, taking into consideration the importance of the drug to the patient.

**SUPPLEMENTARY INFORMATION**

This supplementary information is not to be used in the absence of medical advice or consultation with your healthcare provider. This information should not be used in place of advice from your healthcare provider in the treatment of any health problem. This information is intended to provide general information on the subject(s) covered, and is not meant to replace advice from your healthcare provider.

**Regulatory Information**

Erosive Esophageal Healing Rates

<table>
<thead>
<tr>
<th>Best Possible Cys</th>
<th>Ranitidine 30 mg b.i.d.</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week (N=20)</strong></td>
<td><strong>Ranitidine 30 mg</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>2</td>
<td>58.8%**</td>
<td>38.8%**</td>
</tr>
<tr>
<td>4</td>
<td>91.4%**</td>
<td>72.5%**</td>
</tr>
</tbody>
</table>

**Cys** indicates a significant difference from placebo.

In this study, all PREVACID® group reported significantly better relief of heartburn and less day and night inhibition than in 2 tests done with 4 different degrees of in patients with erosive esophagitis. In a dose of 30 mg was significantly more effective than ranitidine 150 mg b.i.d. as shown below.

Erosive Esophageal Healing Rates

**PREVACID** 30 mg (N=20) | Ranitidine 30 mg b.i.d. (N=20) | Placebo (N=20)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week (N=11)</strong></td>
<td><strong>Ranitidine 30 mg</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>2</td>
<td>62.5%**</td>
<td>45.8%**</td>
</tr>
<tr>
<td>4</td>
<td>82.5%**</td>
<td>65%**</td>
</tr>
<tr>
<td>6</td>
<td>85%**</td>
<td>69%**</td>
</tr>
</tbody>
</table>

**Cys** indicates a significant difference from placebo.

In addition, patients treated with PREVACID reported less day and night inhibition and less heartburn for fewer days than patients taking ranitidine 150 mg b.i.d.

Although this study demonstrates effectiveness of PREVACID in healing erosive esophagitis and shows that the recommended dose for erosive esophagitis is 150 mg b.i.d., the dose used in the study is 30 mg.

Long-Term Maintenance Treatment of Erosive Esophagitis

Two independent, double-blind, multicenter, controlled trials were conducted in patients with erosive esophagitis. The patients treated with PREVACID, ranitidine, and placebo were included in the trial and followed for one year after treatment.

Endoscopic Remission Rates

**Drug** | **Patients in Endoscopic Remission**
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine 30 mg b.i.d. (N=50)</td>
<td>80%</td>
</tr>
<tr>
<td>Ranitidine 150 mg b.i.d. (N=50)</td>
<td>76%</td>
</tr>
</tbody>
</table>

Ranitidine 30 mg b.i.d. was superior to ranitidine 150 mg b.i.d. in the treatment of erosive esophagitis and was significantly effective in the maintenance of remission.

Carboxyhemoglobin, Mutagenesis, Impairment of Fertility

In two independent, double-blind, randomized studies in patients with erosive esophagitis, PREVACID was shown to be effective in reducing the absorption of drugs that affect the health of the male or female organ.

Carboxyhemoglobin levels were measured in patients with erosive esophagitis who were treated with either PREVACID or placebo. The results showed that PREVACID significantly reduced the levels of carboxyhemoglobin in patients with erosive esophagitis.

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APPLICATION NUMBER:
NDA 20-406/S024

MEDICAL REVIEW(S)
I. Background and Introduction

Lansoprazole (PREVACID® Delayed-Release Capsules, pronounced pre'-va-sid, AG-1749, TAP Holdings Inc.), has been approved for a number of clinical indications, the first on 10 May 1995 for short-term, up to 4 weeks, treatment by oral dosage of 15 mg once daily before eating for healing of active duodenal ulcer; for doses of 30 mg once daily before eating for up to 8 weeks for healing of erosive esophagitis (plus an additional 8 weeks if not healed or recurrent); and for 60 or more mg/day indefinitely for the Zollinger-Ellison syndrome or other pathological hypersecretory conditions (divided doses are recommended for over 120 mg/day). Other approvals have been granted since then, for use of lansoprazole for maintenance of healing of
errosive esophagitis (as of 8 April 1995), maintenance of healing of duodenal ulcers, 17 April 1997; healing of gastric ulcer, 8 May 1997; short-term treatment of symptoms of gastroesophageal reflux disease (GERD), 12 March 1998. In addition, lansoprazole was considered “approvable” on 11 May 1998 for eradication of gastric mucosal infection with Helicobacter pylori (Hp) when used along with amoxicillin and clarithromycin.

As a results of these approvals in the United States, and the registration of lansoprazole for treatment of these problems in most of the countries of the world, hundreds of thousands of people, now millions, have been taking the drug, some for periods of more than a year (exact figures not available), and spontaneous reports of adverse effects are accumulating. Among these that have not been previously specified in the ADVERSE REACTIONS section are “blurred vision” in the subsection on Special Senses, “anaphylactoid-like reaction” in the subsection on Body as a Whole, and pancreatitis in the subsection on Digestive System. Concern about these problems was expressed in a letter to the sponsor dated 9 October 1997 making mention of 10 reported cases of anaphylactic and anaphylactoid-type reactions, 4 reported cases of blurred vision, and 4 cases of pancreatitis. The sponsor’s reply to that letter is the subject of this submission.

II. Sponsor’s Proposed Labeling Changes

The letter of 9 January 1998 from the sponsor proposed that changes be made to the labeling in the ADVERSE REACTIONS section as follows:

1) Add, in subsection on Body as a Whole, “anaphylactoid-like reaction;”
2) Substitute “blurred vision” for “amblyopia” in the subsection on Special Senses;
3) No addition of “pancreatitis” in the subsection on Digestive System.

Justifications were provided in the letter from the sponsor for these proposed changes, in which it was agreed that addition of “anaphylactoid-like reactions” was appropriate, but argued that their analysis of the reported cases of pancreatitis suggested that alcohol abuse, history of chronic pancreatitis, use of other medications were more likely causes than lansoprazole. It was further submitted that the term “blurred vision” was more accurate to describe the symptoms reported as “eyes blurry,” “blurry vision,” and “blurred vision.” They argued that “amblyopia” was a misleading term, in that it implies an event much broader in scope and more severe than the four cases reported.

Comment: Although the cases of acute pancreatitis reported may have been caused by something other than lansoprazole, which the sponsor claims to be the case, this problem will need to be watched carefully. For the moment, it may be reasonable to accept the sponsor’s argument that it is not clearly a lansoprazole-induced complication. It is true that vast numbers of people do abuse alcohol, and that in the United States alcohol abuse is the leading cause of both acute and chronic pancreatitis. It will need to be determined if taking lansoprazole induces an increased risk above that in people not taking lansoprazole. This is admittedly very difficult to ascertain when only spontaneous reports are available. Pancreatitis was not noted in the preclinical
studies in animals (see pharmacology/toxicology review of NDA 20-406 by Dr. Y. Chopra, 9
January 1995, and medical review by Dr. H. Gallo-Torres, 15 September 1994)

With respect to the question of amblyopia vs blurred vision, it may be more likely that patients as
well as physicians understand the latter term better than the rather pedantic, Greek-derived term
"ambly-opia" that means dullness-vision/eye defect. The sponsor's suggestion to substitute the
more common term is acceptable. However, it must be noted that a recent case of blindness was
reported to MedWatch by the sponsor initially on 2 April 1998. This occurred in a 64-year-old
male ( ) who experienced loss of vision in his left eye after a first dose
of PREVACID 15 mg on 23 March, and then in the right eye after a second dose the following
day. A follow-up report was received on 18 May, in which the sponsor reported that after the
patient had been hospitalized 25-31 March for treatment with intravenous cortisone and
subsequent oral cortisone 20 mg t.i.d., there was later improvement in vision but residual
peripheral field loss. We shall initiate a search of the spontaneous adverse event reporting
system to investigate all effects on visual function, minor or major, in patients taking
lansoprazole. The question of proton-pump inhibitors on rare occasions causing vision problems
has been raised before with respect to omeprazole in the German literature, although contested
(see Leber Magen Darm 1995; 25:6-8, 39, 152-5).

III. Regulatory Recommendations

It is recommended that the labeling changes proposed by the sponsor be implemented at the next
opportunity for printing and distribution of revised labeling. It is further recommended that the
sponsor be asked to provide followup on the case of blindness initially reported in April of this
year, and that a consultation request be forwarded to the Division of Pharmacovigilance and
Epidemiology for a search of the adverse event reporting system database for all cases of visual
disturbance in patients taking lansoprazole, as well as for cases of pancreatitis.

John R. Senior, M.D., Medical Officer
Division of Gastrointestinal & Coagulation Drug Products

cc:
NDA 20-406, SLR-024
HFD-180
HFD-180/LTalarico
HFD-180/JGallo-Torres
HFD-180/JSenior
HFD-180/JChoudary
HFD-180/EDuffy
HFD-181/CSO
Division of Gastrointestinal & Coagulation Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-406/SLR-024

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

JUL 22 1998

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): July 14, 1998

Receipt Date(s): July 15, 1998

Background and Summary Description: Supplement 024 provides for the following changes to the ADVERSE REACTIONS section of the package insert: addition of “anaphylactoid-like reaction” under the subheading Body as a Whole, and the substitution of “blurred vision” for “amblyopia” in the subheading, Special Senses.

This supplement was approved on June 23, 1998 with draft labeling (as submitted in the original supplement dated January 12, 1998). The sponsor has submitted final printed labeling (FPL) in response to the approval letter.

Review

The submitted FPL, identified as “03-4891-R11-Rev.June, 1998,” was compared to the original draft labeling and is acceptable. The FPL also contains the changes approved in supplement 021 on July 20, 1998.

Conclusions

The FPL is acceptable and should be acknowledged and retained.

Maria Walsh  7/22/98
Maria R. Walsh, M.S.  
Regulatory Project Manager
cc:
    Original NDA 20-406/S-024
    HFD-180/Div. Files
    HFD-180/PM/M.Walsh
    HFD-180/L.Talarico

final: M.Walsh 7/22/98
filename: 20406S24807.rev2.doc

PM REVIEW
Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-406/SLR-024

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

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): January 9, 1998

Receipt Date(s): January 12, 1998

Background and Summary Description: Supplement 024 provides for the following changes to the ADVERSE REACTIONS section of the package insert: Addition of "anaphylactoid-like reaction" under the subheading, Body as a Whole and the substitution of "blurred vision" for "amblyopia" under the subheading, Special Senses.

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). The following differences were noted.

1. ADVERSE REACTIONS:

   A. The term "anaphylactoid-like reaction" was added under the subheading, Body as a Whole.

   B. The term "blurred vision" was substituted for the term "amblyopia" under the subheading, Special Senses.

These revisions are recommended for approval per the Medical Officer's review dated June 19, 1998.

2. In addition, the revisions approved on March 12, 1998 in supplement 016 do not appear in the draft labeling. These revisions include addition of the term "speech disorder" under the subheading, Special Senses, and the term "urinary retention" under the subheading, Urogenital System under the ADVERSE REACTIONS section; and revisions to the CLINICAL STUDIES, INDICATIONS, and DOSAGE AND ADMINISTRATION which reflect the addition of a new indication for symptomatic gastroesophageal reflux disease (GERD).
These revisions were approved on March 12, 1998 in supplement 016 and must appear in the final printed labeling (FPL) to be submitted for this supplement.

Conclusions

1. The labeling revisions proposed in this supplement have been recommended for approval by the Medical Officer (see Medical Officer review dated June 19, 1998).

2. The labeling revisions approved on March 12, 1998 in supplement 016 must be included in the FPL to be submitted for this supplement.

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

cc:
Original NDA 20-406/S-024
HFD-180/Div. Files
HFD-180/M.Walsh

final: M.Walsh 6/23/98
filename: 20406S24-rev806.doc

CSO REVIEW
TAP Holdings, Inc.
Attention: Gary C. Magistrelli, Ph.D.
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Magistrelli:

We acknowledge the receipt of your July 14, 1998 submission containing final printed labeling in response to our June 23, 1998 letter approving your supplemental new drug application for Prevacid (lansoprazole) Delayed-Release Capsules.

We have reviewed the labeling that you submitted in accordance with our June 23, 1998 letter, and we find it acceptable.

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

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
NDA 20-406/S-024
Page 2

cc:
Archival NDA 20-406/S-024
HFD-180/Div. Files
HFD-180/M.Walsh
HF-2/Medwatch (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-95/DDMS (with labeling)
HFD-613/OGD (with labeling)
HFD-735/OPDRA (with labeling)
DISTRICT OFFICE

final: M.Walsh 7/22/98
filename: 20406S24807.A&R.doc

ACKNOWLEDGE AND RETAIN (AR)
July 14, 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
560 Fishers Lane
Rockville, MD 20857

Attn: Lilia Talarico, M.D.
   Director

RE: PREVACID® (lansoprazole) Delayed-Release Capsules
    Addition/Substitution to the ADVERSE REACTIONS Section
    FPL for Approved Supplement NDA 20-406/S-024

Dear Dr. Talarico:

TAP Holdings submits this Final Printed Labeling (FPL) to the supplemental
new drug application for PREVACID.

Reference is made to the Agency’s letter dated June 23, 1998, which stated
that this supplemental application was approved. Enclosed are 20 copies of
the final printed labeling, ten of which are individually mounted on heavy-
weight paper.

Please do not hesitate to contact me at the number listed below should
additional information be needed.

Sincerely,

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