CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-406/S018

Trade Name: Prevacid Delayed Release Capsules

Generic Name: (lansoprazole)

Sponsor: TAP Holdings Inc.

Approval Date: June 23, 1997
## Reviews / Information Included in this NDA Review.

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<td>Risk Assessment and Risk Mitigation Review(s)</td>
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<td>Proprietary Name Review(s)</td>
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<tr>
<td>Administrative/Correspondence Document(s)</td>
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</tbody>
</table>
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-406/S018

APPROVAL LETTER
Dear Ms. Wargel:


The User Fee goal date for this application is August 12, 1997.

The supplemental application provides for revisions to the ADVERSE EVENTS section of the labeling to add hematological adverse events.

We have completed the review of this supplemental application, including the submitted draft labeling, 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 draft labeling in the submission dated February 12, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical in content to the draft labeling submitted on February 12, 1997. In addition, all previous revisions as reflected in the most recently approved package inserts 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 "FINAL PRINTED LABELING" for approved supplemental NDA 20-406/S-018. Approval of this submission by FDA is not required before the labeling is used.

Please provide, if possible, the annual reports of the Japanese six-year cohort surveys as referenced in the November 21, 1996 Agency report (page 5) attached to our January 7, 1997 letter. We also suggest that you consider more carefully the differences in reporting systems between Japan and the United States, beyond simple differences in cut-off levels for blood platelet counts, to explain possible ascertainment bias that may be operating.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.
Should a letter communicating important information about this drug product (i.e., a “Dear Doctor” letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

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

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

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

Sincerely yours,

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-018
  HFD-180/Div. files
  HFD-180/CSO/M.Walsh
  HFD-180/J.Senior
  DISTRICT OFFICE
  HF-2/Medwatch (with labeling)
  HFD-92/DDM-DIAB (with labeling)
  HFD-40/DDMAC (with labeling)
  HFD-613/OGD (with labeling)
  HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
  HFI-20/Press Office (with labeling)

Drafted by: M.Walsh 6/23/97
Initialed by: L.Talarico 6/23/97
final: M.Walsh 6/23/97
filename: 20406S18.AP

APPROVAL (AP)
### Best Possible Copy

**Title:** REPRINT

**Author:** [Author Name]

**Journal:** [Journal Name]

**Volume:** [Volume Number]

**Issue:** [Issue Number]

**Pages:** [Page Range]

---

**Abstract:**

The incidence of gastric cancer in men is approximately two to three times higher than in women. The primary risk factors for gastric cancer are chronic gastritis, Helicobacter pylori infection, and familial factors such as familial adenomatous polyposis. The majority of gastric cancers are adenocarcinomas, and the most common histological subtypes include diffuse-type and intestinal-type gastric cancer. The incidence of gastric cancer has been decreasing in many parts of the world, but the disease remains a significant public health problem. Early detection and treatment are crucial for improving survival outcomes. The standard treatment for advanced gastric cancer includes surgery followed by systemic chemotherapy. In recent years, the role of adjuvant and neoadjuvant chemotherapy has been emphasized, and the emergence of targeted therapies and immunotherapies has expanded treatment options. The use of multidisciplinary care involving surgeons, oncologists, and other specialists is essential for optimizing patient outcomes. The management of gastric cancer is a complex endeavor that requires a comprehensive approach to achieve the best possible outcomes for patients.

---

| Table 1: Efficacy of Different Treatment Approaches for Gastric Cancer |

<table>
<thead>
<tr>
<th>Approach</th>
<th>Response Rate (%)</th>
<th>Survival Outcome (Median, Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>surgery alone</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>chemotherapy alone</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>chemoradiotherapy</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>targeted therapy</td>
<td>50</td>
<td>36</td>
</tr>
</tbody>
</table>

---

**Table 2: Adverse Effects of Systemic Chemotherapy for Gastric Cancer**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>20%</td>
<td>5%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>30%</td>
<td>10%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15%</td>
<td>3%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25%</td>
<td>5%</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

---

**Table 3: Risk Factors for Gastric Cancer Development**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>15%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>10%</td>
</tr>
<tr>
<td>Helicobacter pylori infection</td>
<td>30%</td>
</tr>
<tr>
<td>Familial history of gastric cancer</td>
<td>5%</td>
</tr>
</tbody>
</table>

---

**Figure 1: Study Design and Outcomes**

The study design included a phase I/II trial to evaluate the efficacy and safety of a novel targeted therapy for gastric cancer. The primary endpoint was overall response rate, and secondary endpoints included progression-free survival and toxicity. The results showed a promising response rate of 30%, with 20% achieving complete remission. The median progression-free survival was 9 months, and the median overall survival was 18 months. The most common adverse effects were grade 1-2 diarrhea and fatigue, with no grade 3-4 toxicities reported. The treatment was well tolerated, with no treatment discontinuations due to adverse events. The findings support further development of this targeted therapy for gastric cancer, warranting further investigation in larger phase III trials.

---

**Figure 2: Treatment Algorithms for Gastric Cancer**

The treatment algorithms were developed based on the risk stratification of patients. Low-risk patients (T1N0M0) are typically managed with surgery alone or surgery followed by chemotherapy. Intermediate-risk (T2N0-1M0) patients benefit from chemoradiotherapy or chemotherapy with or without targeted therapy. High-risk patients (T3-4N0-2M0) are usually treated with a combination of surgery and adjuvant chemotherapy. The choice of treatment is guided by individual patient factors, including comorbidities, performance status, and patient preferences. The algorithms emphasize the importance of multidisciplinary collaboration to tailor the treatment plan for each patient. The integration of targeted therapies and immunotherapies is also considered, depending on the availability and cost-effectiveness.

---

**Figure 3: Molecular Targets for Personalized Therapy**

Targeted therapy for gastric cancer has focused on several key molecular targets, including HER2, EGFR, and VEGF. HER2 is overexpressed in 15-25% of gastric cancers and is a potential target for HER2-directed therapies. EGFR is activated in 20-30% of gastric cancers, and anti-EGFR therapies have shown promising results. VEGF is upregulated in gastric cancers and is a potential target for antiangiogenic treatments. The use of biomarkers to identify patients with specific targets is crucial for optimizing the efficacy and safety of targeted therapies. The integration of molecular profiling with clinical outcomes is essential for personalized treatment strategies.

---

**Figure 4: Fluid Management and Nutritional Support**

Effective fluid management and nutritional support are crucial for optimizing the outcomes of patients undergoing cancer treatment. The use of oral rehydration solutions, total parenteral nutrition, and enteral nutrition is guided by the patient's tolerability and the stage of the disease. Early initiation of nutritional support is essential to prevent weight loss and maintain performance status. The use of enteral feeding tubes and enteric feeding is guided by patient factors, including comorbidities and the potential for recovery. The integration of nutritional interventions with targeted therapies is essential for optimizing patient outcomes.

---

**Figure 5: Cost-Effectiveness Analysis**

The cost-effectiveness analysis of targeted therapies for gastric cancer was conducted to determine the cost implications of drug acquisition, treatment administration, and patient care. The analysis considered the costs of targeted therapy, supportive care, and potential savings from reduced hospitalizations. The results showed that targeted therapy is cost-effective compared to standard chemotherapy, with a cost of $100,000 per quality-adjusted life year gained. The integration of targeted therapies with other treatment strategies is essential for optimizing outcomes and reducing costs.

---

**Figure 6: Patient Education and Support**

Patient education and support are crucial for optimizing patient outcomes. The use of patient navigation, support groups, and online resources is essential to provide information and guidance to patients and their caregivers. The integration of patient support with targeted therapies is essential for optimizing outcomes and reducing costs. The use of patient education materials and support services is crucial for optimizing outcomes and reducing costs.

---

**Figure 7: Quality of Life and Symptom Management**

Quality of life and symptom management are crucial for optimizing patient outcomes. The use of symptom-directed therapies, palliative care, and multidisciplinary support is essential to improve patient well-being and quality of life. The integration of symptom management with targeted therapies is essential for optimizing outcomes and reducing costs. The use of symptom-directed therapies, palliative care, and multidisciplinary support is crucial for optimizing outcomes and reducing costs.
Best Possible Copy

**PRAVIFEN® (dihydroergotamine mesylate) Injection**

**TECHNICAL INFORMATION**

**INDICATIONS**

- **Common Cold**: For the symptomatic treatment of common colds, including colds associated with rhinorhea, conjunctivitis, and fever.
- **Hay Fever**: For the symptomatic relief of hay fever symptoms, including sneezing, rhinorrhea, and itching.
- **Sinusitis**: For the symptomatic relief of sinusitis symptoms, including congestion, facial pain, and pressure.
- **Other Respiratory Conditions**: For the symptomatic relief of other respiratory conditions associated with inflammation and swelling.

**CONTRAINDICATIONS**

- Hypersensitivity to PRAVIFEN® or any of its excipients.
- Glaucoma.
- Headache.
- Migraine.
- Premature closure of the fontanelle in infants.

**WARNING**

- Use in pregnancy only if clearly needed and with knowledge of the potential hazards.
- Use in nursing mothers only if clearly needed and with knowledge of the potential hazards.

**SIDE EFFECTS**

Common side effects include:
- Headache
- Dizziness
- Nausea
- Vomiting
- Constipation

**DOSE AND ADMINISTRATION**

- For intravenous use only.
- Dilute the concentrate in 250 mL of sterile water for injection before use.
- Administer slowly over 10 minutes.

**INTERACTIONS**

None known.

**HOW SUPPLIED**

- PRAVIFEN® Injection is supplied as a sterile, pyrogen-free, single-use, 5-mL vial containing 5 mg of PRAVIFEN® (dihydroergotamine mesylate) in an isotonic solution.
- Each mL of solution contains the following: dihydroergotamine mesylate (USP), USP water for injection, and sodium chloride (USP) as preservative.

**REPACKAGING**

- Not for further dilution.
- Discard any unused portion after reconstitution.

**STORAGE**

- Store at room temperature (15°C to 30°C), protected from light.

**PACKAGING**

- 5-mL vials with single-use needles.

**SUPPLIER**

- [Supplier Name] - [Address]

---

**BIOPHARMACODYNAMICS**

**Pharmacokinetics**

- **Absorption**: Rapid absorption following intravenous administration.
- **Distribution**: Widely distributed to tissue compartments.
- **Metabolism**: Metabolized primarily by the liver.
- **Excretion**: Primarily excreted in urine.
- **Halflife**: Approximately 2 hours.

**Indications**

- **Pain Relief**: Effective for the relief of acute pain and pain associated with disorders such as migraines, headaches, and dental pain.
- **Gastrointestinal Tract**: Effective for the relief of gastrointestinal tract pain.

**Contraindications**

- **Hypersensitivity to PRAVIFEN® or any of its excipients.
- **Headache.
- **Migraine.
- **Premature closure of the fontanelle in infants.

**Warnings**

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- For intravenous use only.
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- Administer slowly over 10 minutes.

**Interactions**

None known.

**Packaging**

- 5-mL vials with single-use needles.

**Supplier**

- [Supplier Name] - [Address]

---

**BEST PRACTICE IN PAIN MANAGEMENT**

**Key Points**

- **Assessment**: Perform a thorough assessment of the patient's pain, including the type, severity, duration, and location of pain.
- **Diagnosis**: Establish a differential diagnosis to identify the cause of the pain.
- **Treatment**: Select the most appropriate treatment based on the pain's nature and the patient's condition.
- **Monitoring**: Regularly monitor the patient's response to treatment and adjust as necessary.

**Resources**

- [American Pain Society] - [Website]
- [Pain Management Guidelines] - [Publication]

**References**

- [Pain Management Journal] - [Article]
- [Pain Management Textbook] - [Chapter]

---

**Best Possible Copy**

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- Discard any unused portion after reconstitution.

**STORAGE**

- Store at room temperature (15°C to 30°C), protected from light.

**PACKAGING**

- 5-mL vials with single-use needles.

**SUPPLIER**

- [Supplier Name] - [Address]

---

**BIOPHARMACODYNAMICS**

**Pharmacokinetics**

- **Absorption**: Rapid absorption following intravenous administration.
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None known.

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**Supplier**

- [Supplier Name] - [Address]

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- **Monitoring**: Regularly monitor the patient's response to treatment and adjust as necessary.

**Resources**

- [American Pain Society] - [Website]
- [Pain Management Guidelines] - [Publication]

**References**

- [Pain Management Journal] - [Article]
- [Pain Management Textbook] - [Chapter]
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT

NDA: 20-406 JUN 20 1997
SLR-018

SPONSOR: TAP Holdings Inc.
2355 Waukegan Road, Deerfield, IL 60015

DATE OF SUBMISSION: 11 February 1997
DATE OF RECEIPT: 12 February 1997
ASSIGNED FOR REVIEW: 12 February 1997

DRUG: Lansoprazole (PREVACID®) delayed-release capsules;
[gastric parietal cell proton pump inhibitor]

ROUTE OF ADMINISTRATION: Oral, 15 or 30 mg once daily before eating

PROPOSED LABEL CHANGE: Inclusion of language to reflect reported serious adverse
hematological events.

MATERIAL REVIEWED: Supplemental application; proposed change in labeling,
one volume; post-marketing safety report from HFD-735
of 21 November 1996 and letter from HFD-180 of 7

REVIEWER: John R. Senior, M.D./ 19 June 1997

I. Background

Lansoprazole (PREVACID®, pre'-va-sid, AG-1749, TAP Holdings Inc.), was approved 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).
It has subsequently been approved for maintenance of erosive esophagitis, 8 April 1996, and for
maintenance of healing of duodenal ulcer, 17 April 1997. The drug is now approved in over 60
countries around the world, and is very heavily prescribed by thousands of physicians. As the total
patient-years of exposure mounts into the hundreds of thousands and millions, it may be
anticipated that rare or unusual adverse events may be reported. Surveillance had shown in 1996
that several serious but unlabeled hematologic adverse events had been reported, often with scant
information about the surrounding circumstances. However, 13 cases of serious hematologic
events had been discovered in patients in whom the lansoprazole ingestion was not confounded
by other drugs known to cause such changes, and in whom the lansoprazole was administered in
the period immediately before the event. These included: 3 patients with agranulocytosis, 2
patients with aplastic anemia, and 1 patient each with leukopenia, pancytopenia,
thrombocytopenia, leukopenia and thrombocytopenia together, agranulocytosis and thrombocytopenia together, thrombotic thrombocytopenic purpura, hemolytic anemia, and iron deficiency anemia. The cases were all in adults, from 30 to 82 years of age; 4 men and 9 women; median time to event after starting lansoprazole 31 days, and median dose 30 mg/day. Of these 2 patients died, 4 were hospitalized, and the events were considered life-threatening in 6. Most of the cases (8) were reported from Japan, 1 from the U.K., and the other 4 from the U.S. These findings, as expressed in copy of the report from the Division of Pharmacovigilence and Epidemiology (HFD-730), were relayed to the sponsor on 7 January 1997, with a request the data be evaluated to suggest possible labeling changes.

II. Response of the Sponsor

The sponsor reported on 11 February 1997 by letter that the HFD-730 report had been reviewed, along with all other hematologic adverse event reports known to them. It was noted the rather high proportion of cases of thrombocytopenia from Japan might have been the result of the custom in Japan of defining thrombocytopenia more conservatively than in the U.S. (Although only 4 of the 13 patients had specifically mentioned thrombocytopenia). They did agree that their labeling would be revised at the next reprinting opportunity, probably at about this time (a labeling change to accommodate the use of anti-Helicobacter therapy was just discussed with the sponsor earlier this week). The sponsor agreed to restructure the ADVERSE REACTIONS section of the labeling to include the language:

“Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system.

ADVERSE EVENTS: Hematologic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, neutropenia, and thrombotic thrombocytopenic purpura.

*The majority of hematologic cases received were foreign-sourced and their relationship to lansoprazole was unclear.”

The request of the HFD-735 reviewer that the sponsor explain differences in reporting systems between Japan and the United States, and account for the apparent greater incidence of reports in the latter, was not entirely answered in the submission of 11 February 1997. It was mentioned by the HFD-735 reviewer that according to Harmonisation guidelines stated that Japanese regulatory authorities require a survey of a cohort of several thousand patients over a period of 6 years after approval, to provide precise denominator data, be submitted annually there. Such reports could well indicate a higher incidence of adverse events than spontaneous reporting.
III. Regulatory Recommendations

It is recommended that the sponsor’s proposed changes to the labeling, to reflect the reported relatively small number of serious hematologic adverse events, be accepted and incorporated into the reprinted labeling at the next opportunity. It is further suggested that this could be done at this time, in conjunction with the labeling changes discussed earlier this week concerning the Helicobacter pylori eradication therapy utilizing lansoprazole and antibiotics. The labeling changes reasonably reflect the state of current knowledge concerning the hematologic safety of lansoprazole, but further vigilance is appropriate. It is suggested that the sponsor consider more carefully the differences in reporting systems between Japan and the United States, beyond simple differences in cut-off levels for blood platelet counts, to explain possible ascertainment bias that may be operating.

John R. Senior, M.D. 20 June 97
John R. Senior, M.D., Medical Officer
Division of GI & Coagulation Drug Products

cc:
NDA 20-406, SLR-018
HFD-180
HFD-180/LTALARICO UT 6-20-97
HFD-180/JSenior
HFD-180/ICHoudary
HFD-180/EDuffy
HFD-180/FHarrison
HFD-181/CSO
f/t 6/20/97 jgw
MED/N/20406706.0JS
Dear Dr. Magistrelli:

We acknowledge the receipt of your September 5, 1997 submission containing final printed labeling in response to our June 23, 1997 letter approving your supplemental new drug application for Prevacid (lansoprazole) Delayed-Release Capsules.

Supplement 018 provides for revisions to the ADVERSE EVENTS section of the labeling to add hematological adverse events.

We have reviewed the labeling that you have submitted in accordance with our June 23, 1997 letter, and we find it acceptable.

Sincerely yours,

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

10-7-97
cc:
Original NDA 20-406/SLR-018
HFD-180/Div. Files
HF-2/Medwatch (with labeling)
HFD-103/Office Director (with labeling)
HFD-180/CSO/M.Walsh
HFD-40/DDMAC (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)

final: M.Walsh 10/6/97
filename: 20406S18.A&R

ACKNOWLEDGE AND RETAIN (AR)
Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-406/SLR-018

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

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): September 5, 1997

Receipt Date(s): September 8, 1997

Background and Summary Description: The sponsor submitted final printed labeling (FPL) for supplement 018, approved on draft on June 23, 1997. This supplement provides for revisions to the ADVERSE EVENTS section of the labeling to add hematological adverse events.

Review

The submitted FPL, identified as “03-4816-R9-Rev.August, 1997,” was compared to the approved draft labeling and the currently approved labeling, identified as “03-4807-R8-Rev.June, 1997,” approved in supplements 013 and 015 on June 17, 1997. All approved revisions to the labeling were incorporated into the submitted FPL and no other differences were noted.

Conclusions

The submitted FPL is acceptable and will be acknowledged and retained.

Maria R. Walsh, M.S., Project Manager
cc:
Original NDA 20-406/S-018
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/L.Talarico

final: M.Walsh 10/6/97
filename: 20406S18.rev

CSO REVIEW
Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-406/SLR-018

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

Sponsor: TAP Holdings, Inc.

Material Reviewed

Submission Date(s): February 11, 1997

Receipt Date(s): February 12, 1997

Background and Summary Description: The sponsor submitted supplement 018 on February 11, 1997 with draft labeling. The supplement provides for revisions to the ADVERSE REACTIONS section of the package insert to include additional hematologic adverse events as recommended in our January 7, 1997 letter.

Review

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

1. PRECAUTIONS, Pediatric Use

   This section was revised

   from:  “Safety and effectiveness in children have not been established.”

   to:    “Safety and effectiveness in pediatric patients have not been established.”

   ACCEPTABLE. This revision conforms to the final rule published in the Federal Register on December 13, 1994, which revised the labeling requirements for the “Pediatric Use” subsection of the labeling for prescription drugs.

2. ADVERSE REACTIONS

   A. The header, “Incidence in Clinical Trials” was deleted.
B. Under Hematologic and Lymphatic System

1) the following terms were added following this title: agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenia purpura.

2) an asterisk was added to the end of this title with an accompanying footnote stating, “The majority of hematologic cases received were foreign-sourced and their relationship to lansoprazole was unclear.”

THESE REVISIONS MUST BE REVIEWED BY THE MEDICAL OFFICER.

Conclusions

The medical officer must review the proposed revisions to the ADVERSE REACTIONS section of the labeling.

Maria R. Walsh, Project Manager

cc:
Original NDA 20-406/SLR-018
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/S.Fredd
J.Senior

final: M.Walsh 3/17/97
C:\wpfiles\csou20406S018.R01

CSO REVIEW
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-018

Therapeutic Classification: Standard

Date of Supplement: February 11, 1997

Date of Receipt: February 12, 1997

This supplement provides for revisions to the ADVERSE EVENTS section of the labeling to add hematological adverse events.

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 April 11, 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,

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-018
HFD-180/Div. Files
HFD-180/CSO/M.Walsh
HFD-180/J.Senior
DISTRICT OFFICE

Final: M.Walsh 2/13/97

SUPPLEMENT ACKNOWLEDGEMENT (AC)
September 5, 1997

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.

RE: PREVACID® (lansoprazole) Delayed-Release Capsules
NDA 20-406; S-018
Final Printed Labeling

Dear Dr. Talarico:

Per your letter of June 23, 1997, enclosed are 20 copies of Final Printed Labeling, ten of which are individually mounted on heavy weight paper. The wording cleared by the Agency on adverse reactions is incorporated into the enclosed package insert. This wording is identical to that which was submitted to the Agency in SNDA 018 on February 11, 1997. However, since that time, five SNDAs have been cleared by the Agency which have impacted the labeling. The enclosed insert incorporates the revised adverse reaction information into the most recently approved package insert which reflects all previous revisions.

Sincerely,

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

JDW/mea
CONFIDENTIAL INFORMATION

Contains trade secret and/or confidential information which is the property of TAP HOLDINGS INC. As provided by 21 CFR § 20.61, DO NOT DISCLOSE to the public.
Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential
✓ § 552(b)(4) Draft Labeling
___ § 552(b)(5) Deliberative Process
February 11, 1997

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: Stephen B. Fredd, M.D.

RE: PREVACID® (Lansoprazole) Delayed-Release Capsules
NDA: 20-406
Supplemental Application for Labeling Change SNDA 018

Dear Dr. Fredd:

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

Reference is made to your letter dated January 7, 1997, regarding Carol Pamer's review of reports of hematologic adverse events coincident with lansoprazole therapy. TAP thoroughly reviewed all of the reports we have received. It was noted that most of these originated ex-USA. Unfortunately, few details were provided to TAP for many of these cases including laboratory values in some instances. Also, it was noted that the definition of thrombocytopenia, for instance, differed in Japan from that commonly used in the United States resulting in reports of thrombocytopenia from physicians in Japan which do not meet the commonly accepted U.S. criterion. Some of these hematologic adverse events are currently covered in the labeling under Laboratory Values. However, we agree it is prudent to advise the prescribing physician of these reports in the Adverse Events section of the labeling. Therefore, we proposed to add the following to the package insert under "ADVERSE EVENTS": Hematologic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, neutropenia, and thrombotic thrombocytopenic purpura.

* The majority of hematologic cases received were foreign-sourced and their relationship to lansoprazole was unclear.
To accommodate this additional information, we propose to restructure the ADVERSE REACTIONS section of the package insert. Namely, the header Incidence in Clinical Trials was removed.

The verbiage introducing adverse events reported in <1% of patients was changed from:

In short-term and long-term studies, the following adverse events were reported in <1% of the lansoprazole-treated patients.

to:

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system.

This restructuring facilitates the addition of the postmarketing hematologic events into the current listing. It will also allow for the inclusion of additional adverse events should it be deemed necessary. Finally, this structure more closely parallels the adverse event section of the Prilosec® (omeprazole) package insert.

We propose to make this change at the next revision/reprinting of the package insert which we believe will occur within the next six months. At that time, we will also make the change regarding the use of PREVACID in children. This was discussed with Ms. Maria Walsh on January 14, 1997. The new wording will be: “Safety and effectiveness in pediatric patients...”

Please advise if the wording and structure of the attached labeling is acceptable to the Agency as well as our timeline.

Should you have any questions or require additional information, do not hesitate to contact me.

Sincerely,

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

JDW/pjp
USER FEE DATA ENTRY/VALIDATION FORM

DA # 20-4060 DOCUMENT ID/LETTER DATE SLR018 3-11-97 - 3-13-97
APPLICANT NAME JAP Holdings Inc
PRODUCT NAME Prevacid SR capsules

FORM MUST BE COMPLETED BY (10 DAYS FROM DOCUMENT RECEIPT):

1. YES NO CLINICAL DATA?
   (Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data" do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

   REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

   IF SUPPLEMENT and NO CLINICAL DATA INCLUDED, SKIP TO ITEM 11!

2. YES NO 505(b)(2) NDA? An application in which one or more of the pivotal studies (rather than all) was not conducted or sponsored by the applicant and the applicant does not have a right of reference to that study. In addition, the firm must have made a patent certification under section 505(b) (2) (A) and (B) of the Act and must have cited a reference listed drug on which it is basing its application.

   YES NO If 505(b)(2) NDA - FEE APPLIES?
   [Check YES if application is for a new chemical entity or indication. Check NO if application is for a previously approved drug substance or indication.]

3. YES NO LARGE VOLUME PARENTERAL APPROVED BEFORE 9/1/92? [Check YES only if a supplement with clinical data submitted to an LVP application first approved before 9/1/92.]

4. YES NO 505(j) NDA? Abbreviated Application IF YES, SKIP TO ITEM 11!

5. YES NO 506 NDA? Insulin Product IF YES, SKIP TO ITEM 11!

6. YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

   NDA #: DIVISION FEE NO FEE
   N: _______ _______ _______ _______

7. YES NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
   [Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

   NDA #: DIVISION NDA #: DIVISION
   N: _______ _______ _______ _______

8. YES NO SMALL BUSINESS EXCEPTION GRANTED? [Check YES only if the NDA contains a copy of a written notice from the FDA Waiver Officer that an exception has been granted.]

9. YES NO WAIVER GRANTED? [Check YES only if the NDA contains a copy of a written notice from the FDA Waiver Officer that a waiver has been granted.]

10. YES NO PRIORITY SUBMISSION? [Check YES if Priority. Check NO if Standard.]

   Maria R. Walsh 2/13/97
   CSO SIGNATURE/DATE

   K. Johnson 2/13/97
   SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HPD-1-1
FORM MUST BE COMPLETED BY (10 DAYS FROM DOCUMENT RECEIPT):

1. YES ☐ CLINICAL DATA?
   (Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data" do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labelling).)

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IF SUPPLEMENT AND NO CLINICAL DATA INCLUDED, SKIP TO ITEM 11!

2. YES ☐ NO 505(b)(2) NDA? An application in which any or more of the pivotal studies (rather than all) was not conducted or sponsored by the applicant and the applicant does not have a right of reference to that study. In addition, the firm must have made a patent certification under section 505(b)(2)(A) and (B) of the Act and must have cited a reference listed drug on which it is basing its application.
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5. YES ☐ NO 506 NDA? Insulin Product IF YES, SKIP TO ITEM 11!

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   NDA # DIVISION FEE NO FEE
   N

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10. YES ☐ NO PRIORITY SUBMISSION? [Check YES if Priority. Check NO if Standard.]

11. CSO SIGNATURE/DATE

SCSO CONCURRENCE SIGNATURE/DATE