CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-281

MEDICAL REVIEW

APR 2 5 2001

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	21-281
Applicant:	TAP Pharmaceutical Products
Drug:	Lansoprazole (PREVACID®) 15 mg, 30 mg Sachets for suspension [gastric parietal cell proton pump inhibitor][antisecretory] for patients who have difficulty swallowing capsules
Indications:	Healing of erosive esophagitis, maintenance of healing of erosive esophagitis, duodenal ulcer, pathological hypersecretory conditions including Zollinger-Ellison syndrome, *H. pylori*, benign gastric ulcer, and maintenance of healed duodenal ulcer
Administration:	Sachets for oral suspension, 15mg and 30 mg once daily
Material Reviewed:	Application; proposed labeling; clinical pharmacology and biopharmaceutics review; OPDRA Review; DSI biopharm audit; pertinent other information.
Reviewer:	Scheldon Kress, M.D

Brief Overall Summary

The manufacturer proposes to make available several product formulations for those patients who have difficulty swallowing capsules. In addition to the currently approved granules contained in the Prevacid® Delayed-Release Capsules that can be added to food, the manufacturer would like to market Sachets (unit-dose packets) containing 15 or 30 mg granules of lansoprazole plus flavoring granules to mix with water and drink. These granules are identical to those contained in the Prevacid Delayed-Release Capsules currently marketed in the U.S.

The purpose of this review was to establish the bioequivalence of the proposed market formulations of Prevacid® 15 mg and 30 mg sachets and the current market formulations of Prevacid® delayed-Release 15 mg and 30 mg capsules. Based on the information provided in the NDA, the 15 mg and 30 mg Prevacid® sachets for suspension are, respectively, bioequivalent to the currently marketed 15 mg and 30 mg Prevacid® delayed release capsules.

This supplement is approvable, but a number of recommendations are made to the sponsor's revision of the labeling for the 15 mg and 30 mg Prevacid® sachets for oral suspension.

I. Background and Introduction

Lansoprazole (PREVACID®) is a substituted benzimidazole derivative, that suppresses gastric acid secretion via selectively inhibiting the parietal cell membrane (H^+,K^+)-ATPase enzyme system. This pharmacologic effect, "proton pump inhibition" takes place in the gastric parietal cells. This drug is converted in the acidic environment of the gastric parietal cell canaliculi to active sulphenamide derivatives which bind the H^+,K^+-ATPase enzyme system and inhibit the ATP-energy-dependent gastric acid (H^+, proton) secretion mechanism ("pump"), thus inhibiting the final step of acid production.

Prevacid- (Lansoprazole Delayed-Release Capsules) was first approved for use in the U.S. on May 10, 1995. Prevacid is FDA-approved as therapy for use in adults for short-term treatment of active duodenal ulcers; maintenance of healed duodenal ulcers; short-term treatment of active benign gastric ulcer; short- term treatment of symptomatic GERD: short-term treatment and maintenance of healing of erosive esophagitis; and long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome. Prevacid is also indicated for *H. Pylori* eradication to reduce the risk of recurrence of duodenal ulcer as dual therapy in combination with amoxicillin and as triple therapy with amoxicillin and clarithromycin.

Prevacid "Sachets for Suspension" consist of a packet containing lansoprazole 15 or 30 mg in the form of enteric-coated granules and inactive ingredients including sweeteners and flavoring agents. These granules are identical to those contained in the Prevacid Delayed-Release Capsules currently marketed in the U.S. Prevacid Sachets for Suspension are indicated for the same conditions and in the same doses as Prevacid Delayed-Release Capsules.

To form a suspension for oral administration, the contents of each Prevacid unit-dose packet (sachet) should be poured into a container with 2 tablespoons of water, stirred well and consumed immediately. Additional water may be added to the container if granules remain after the initial dosing.

II. Clinical pharmacology/Biopharmaceutics Review

NDA 21-281 submitted for lansoprazole (Prevacid®) 15 mg and 30 mg sachets for suspension, on June 30, 2000, has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics by David G. Udo, Ph.D. The purpose of this review was to establish the bioequivalence of the proposed market formulations of Prevacid® 15 mg and 30 mg sachets and the current market formulations of Prevacid® delayed-Release 15 mg and 30 mg capsules. Based on the information provided in the NDA, the 15 mg and 30 mg Prevacid® sachets for suspension were, respectively, bioequivalent to the currently marketed 15 mg and 30 mg Prevacid® delayed release capsules. Accordingly, the sponsor submitted revision to the Clinical Pharmacology section and other related sections of the approved labeling for the the 15 mg and 30 mg Prevacid® delayed release capsules, to include the 15 mg and 30 mg Prevacid® sachets for suspension in this labeling.

The contents of the sachet is emptied into two tablespoonfuls of water in a suitable container, stirred well and administered immediately to the patient. Two bioequivalence studies (Protocol M98-944 assessing the bioequivalence of the 15 mg Prevacid® sachet and the 15 mg Prevacid® Delayed-Release capsule and Protocol M98-945 assessing the bioequivalence of the 30 mg Prevacid® sachet and the 30 mg Prevacid® Delayed-Release capsule), conducted by the sponsor, were submitted in this NDA.

A satisfactorily validated liquid chromatography/mass spectrometry (LC/MS/MS) method was used in the bioequivalence studies. The acid resistance and dissolution profiles of the lansoprazole granules from the 15 mg and 30 mg Prevacid® sachets were adequately characterized and reasonable dissolution specifications were provided. Since the sachet and the capsule formulations of Prevacid® differ only in the presence of inactive granules in the sachet, the food effects on the sachet and the capsule formulations are expected to be similar. Therefore, a new study of food effect on the sachet formulation was not considered to be necessary.

Based on the data provided in the submitted bioequivalence studies (Protocols M98-944 and M98-945), the proposed market formulations of the 15 mg and 30 mg Prevacid® sachets were, respectively, bioequivalent to the currently marketed formulations the 15 mg and 30 mg the Prevacid® delayed-release capsules. Based on these findings, for both the sachet and capsule formulations of lansoprazole, the systemic drug exposure is highly variable between individuals as evidenced by highly variable $AUC_{infinity}$ and C_{max} . The time to attain maximum drug concentration and elimination half-life is similar for the sachet and capsule formulations of lansoprazole.

The sponsor states that two mild adverse events were observed in Protocol M98-945 and that in both studies (Protocols M98-944 and M98-945), the Prevacid® formulations were safe and well tolerated.

The Biopharm review concluded that the submitted bioequivalence data were deemed acceptable for consideration in the NDA approval process.

However, several issues were raised that needed to be satisfactorily addressed by the sponsor prior to NDA approval. These issues are transcribed below:

1. For each dose unit of the Prevacid® sachet tested for acid resistance and for drug release (NDA Volume 1.11 [pages 044-045]), please provide complete tabulated acid resistance data and tabulated and graphical drug release profile.
2. [redacted]
3. Characterization and quantitation of impurities especially if drug will be utilized by pediatric population.

Additionally, the Biopharm Recommendation was contingent upon a satisfactory report of the DSI Inspection that was ordered by the Agency in connection with this NDA.

III. DSI Biopharm Audit Inspection Review

Michael Skelly, Ph.D., Pharmacologist HFD-48, reported the following conclusion based on his inspection of [redacted]

"We recommend that the data from Study M98-945 be not accepted because neither a reserve sample nor the unused portion of the supplied reference drug was retained for verification at the clinical site, in violation of 21 CFR 320.38 (b) (3)."

Biopharm with concurrence of the GI Division did not agree that approvability should be withheld based upon this violation.

IV. Sponsor's Recommendations for Labeling

The Sponsor's recommended package labeling is:

[redacted]

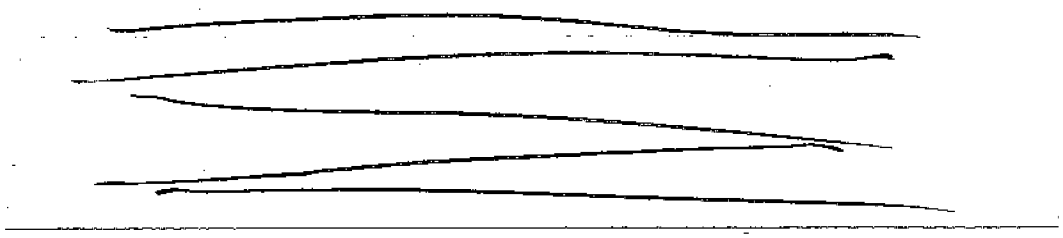
1 page(s) of revised draft labeling has been redacted from this portion of the review.

VI. Medical Officer's Conclusion

Based on the information provided in NDA 21-281, the 15 mg and 30 mg Prevacid® sachets for suspension are, respectively, bioequivalent to the currently marketed 15 mg and 30 mg Prevacid® delayed release capsules. Accordingly, revisions need to be made to the Clinical Pharmacology section of the approved labeling for the 15 mg and 30 mg Prevacid® delayed release capsules, to include the 15 mg and 30 mg Prevacid® Delayed-Release Granules for oral suspension and related statements in other sections of the labeling to include the 15 mg and 30 mg Prevacid® Delayed-Release Granules for oral suspension.

In addition, to make the package insert and container label as accurate and easily understandable as possible and minimize potential user error, I am making the following recommendations:

1 page(s) of revised draft labeling has been redacted from this portion of the review.



Scheldon Kress, M.D.
April 12, 2001

cc:
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-180/SKress
HFD-181/CPerry
N/21281104.0SK

28 page(s) of revised draft labeling has been redacted from this portion of the review.