# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-281**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR 27 2001

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-281

LANSOPRAZOLE (PREVACID®) 15 MG AND
30 MG SACHETS FOR SUSPENSION

TAP PHARMACEUTICAL PRODUCTS, INC.
675 NORTH FIELD DRIVE
LAKE FOREST, IL 60045

REVIEWER: David G. Udo, Ph.D.

ADDENDUM TO PRIMARY REVIEW

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## I. SYNOPSIS/BACKGROUND

NDA 21-281 (original submission) was submitted for Lansoprazole (Prevacid®) 15 mg and 30 mg sachets for suspension, by the sponsor, on June 30, 2000. Prevacid® 15 mg and 30 mg sachets for suspension are proposed for the treatment of adult patients with duodenal ulcers, gastric ulcers, symptomatic gastroesophageal reflux disease (GERD) (see the proposed drug product labeling). The NDA contained two bioequivalence studies: Protocol MS98-944 assessing bioequivalence of the proposed Prevacid® 15 mg sachet for suspension and the approved Prevacid® 15 mg capsule and Protocol MS98-945 assessing bioequivalence of the proposed 30 mg sachet for suspension and the approved Prevacid® 30 mg capsule. Prior to the completion of the review of the NDA, HFD-180 requested the Agency's Division of Scientific Investigations (DSI) to undertake an audit of Protocol MS98-945. This audit culminated in the report submitted by DSI to HFD-180 on March 7, 2001 (Attachment I).

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3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

[redacted]

## IV. RECOMMENDATION

The audit report submitted by the Agency's Division of Scientific Investigations (DSI) to the Division of Gastrointestinal and Blood Coagulation Drug Products (HFD-180) on March 17 2001, in relation to NDA 21-281 (original submission) submitted for lansoprazole (Prevacid®) 15 mg and 30 mg sachets for suspension, by the sponsor, on June 30, 2000, has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The issue raised in the Overall Comment above needs to satisfactorily addressed by the sponsor prior to NDA approval.

Please convey this Recommendation and the Overall Comment above, as appropriate, to the sponsor.

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. _____

cc: NDA 21-281, HFD-180, HFD-180 (Perry), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

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/s/
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David Udo
4/26/01 03:04:46 PM
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APR 27 2001

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-281 SUBMISSION DATE: 03/28/01

LANSOPRAZOLE (PREVACID®) 15 MG AND
30 MG SACHETS FOR SUSPENSION

TAP PHARMACEUTICAL PRODUCTS, INC.
675 NORTH FIELD DRIVE
LAKE FOREST, IL 60045 REVIEWER: David G. Udo, Ph.D.

SUBMISSION TYPE: AMENDMENT (SERIAL #BB) SUBMISSION CODE: 3S

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## I. SYNOPSIS/BACKGROUND

Amendment BB was submitted to NDA 21-281 for Lansoprazole (Prevacid®) 15 mg and 30 mg sachets for suspension, by the sponsor, on March 28, 2001. Prevacid® 15 mg and 30 mg sachets for suspension are proposed for the treatment of adult patients with duodenal ulcers, gastric ulcers, symptomatic gastroesophageal reflux disease (GERD) (see the proposed drug product labeling). In this amendment the sponsor responds to the drug release testing information request contained in the Agency's letter dated March 5, 2001 (see Attachment I).

## II. REVIEW OF SPONSOR'S RESPONSE

**Information Requested in Agency's Letter Dated March 5, 2001**: The sponsor was requested to submit data for *in vitro* dissolution testing of Prevacid® 15 mg and 30 mg sachets for suspension. These were the test formulations in the bioequivalence studies (Protocols M98-944 and M98-945) contained in the original NDA. The sponsor was requested to obtain the dissolution data using [redacted] and a phosphate buffer ([redacted] for the sampling time points of 15, 30, 45 and 60 min. Data were provided previously using [redacted] (the other conditions were unchanged) in the *in vitro* dissolution testing of Prevacid® 15 mg and 30 mg sachets for suspension.

The requested data would be an appropriate justification for the use of [redacted] for *in vitro* dissolution testing of Prevacid® 15 mg and 30 mg sachets instead [redacted] that was used for *in vitro* dissolution testing of Prevacid® 15 mg and 30 mg capsules.

**Sponsor's Response**: The sponsor states (i) that lansoprazole degrades at pH 6.8 and a non-specific method (UV) is needed to quantify both the ionized and unionized species, (ii) that the UV method, which was used for quantifying the lansoprazole content of the

capsules at this pH, could not be used for quantifying the lansoprazole content of the sachets due to interference from the inactive components of the sachets, (iii) that since the lansoprazole content of the sachet could not be quantified by the non-specific method (UV), it became necessary to maintain it in the unionized form and quantify it using a specific analytical method and (iv) that since experiments proved that lansoprazole is stable in this medium, at this pH, was used for dissolution testing of Prevacid® 15 mg and 30 mg sachets for suspension and lansoprazole analysis was performed using

The sponsor then provides the data below demonstrating similarity in the dissolution profiles of lansoprazole granules alone, at pH values of 6.8 for the time points of 30, 45 and 60 min. These data further suggests that for the time points of 45 and 60 min, the dissolution profile of the lansoprazole content of the sachet formulation, at a pH value of 10, is similar to those of lansoprazole granules alone at pH values of 6.8 The dissolution data were obtained using a

for *in vitro* dissolution testing of Prevacid® 15 mg and 30 mg sachets is appropriate.

| Product Analyzed | Paddle Speed (rpm) | Medium pH | Mean (SD) % Drug Release at Each Time-point (min) | | | | n |
|---|---|---|---|---|---|---|---|
| | | | 15 | 30 | 45 | 60 | |
| Lansoprazole Granules Alone | | | 84 (1.2) | 93 (1.8) | 96 (1.0) | 99 (0.9) | 6 |
| Lansoprazole Granules Alone | | | 76 (1.3) | 93 (1.2) | 95 (1.5) | 96 (1.2) | 6 |
| Lansoprazole Granules Plus Inactive Granules | | | 59 (4.3) | 89 (7.5) | 96 (3.7) | 97 (2.8) | 3 |

The sponsor's response seems reasonable. Based on the dissolution data presented above, the following Dissolution Method and Specification are recommended for Prevacid® 15 mg and 30 mg sachets:

Apparatus:
Paddle Rotation Speed:
Medium:

Analytical Method:
Specification:

## III. RECOMMENDATION

Amendment BB submitted to NDA 21-281 for lansoprazole (Prevacid®) 15 mg and 30 mg sachets for suspension on March 28, 2001 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The sponsor has satisfactorily justified the use of [redacted] for the *in vitro* release testing of Prevacid® 15 mg and 30 mg sachets for suspension versus [redacted] for the *in vitro* release testing of Prevacid® 15 mg and 30 mg capsules.

Please convey this Recommendation, as appropriate, to the sponsor.

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. _____

cc: NDA 21-281, HFD-180, HFD-180 (Perry), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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David Udo
4/26/01 03:08:04 PM
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Suresh Doddapaneni
4/27/01 10:39:36 AM
BIOPHARMACEUTICS

Perry

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# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-281 SUBMISSION DATE: 11/30/00

LANSOPRAZOLE 15 MG AND 30 MG
SACHETS FOR SUSPENSION
PREVACID® SACHETS FOR SUSPENSION

TAP PHARMACEUTICAL PRODUCTS, INC.
LAKE FOREST, IL 60045

REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: AMENDMENT #004 SUBMISSION CODE: 3S

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## I. SYNOPSIS/BACKGROUND

Amendment 004 was submitted to NDA 21-281 for lansoprazole (Prevacid®) 15 mg and 30 mg sachets for suspension on November 30, 2000. Prevacid® 15 mg and 30 mg sachets for suspension are proposed for use by patients who have difficulties swallowing the approved Prevacid® 15 mg and 30 mg capsules that are currently on the market. Like Prevacid® 15 mg and 30 mg capsules, Prevacid® 15 mg and 30 mg sachets for suspension are proposed for the following indications:

**Short Term (up to Four Weeks) Treatment of Duodenal Ulcer in Adults**: 15 mg once daily.

***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Reoccurrence in Adults**
**(a) Tripple Therapy with Amoxicillin and Clarithromycin**: 30 mg Prevacid®, 1 g amoxicillin and 500 mg clarithromycin every 12 h for 10-14 days.
**(b) Dual Therapy with Amoxicillin**: 30 mg Prevacid®, 1 g amoxicillin every 8 h for 14 days.

**Maintenance of Healed Duodenal Ulcers in Adults:** 15 mg every 24 h.

**Short Term (up to Eight Weeks) Treatment of Gastric Ulcers in Adults**: 30 mg every 24 h

**Short Term (up to Eight Weeks) Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD) in Adults**: 15 mg every 24 h.

**Short Term (up to Eight Weeks) Treatment of Erosive Esophagitis in Adults**: 30 mg every 24 h.

**Maintenance of Healing of Erosive Esophagitis in Adults:** 15 mg every 24 h.

**Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome in Adults:**

**Recommended Dosage**: 60 mg every 24 h (adjusted to individual patient needs and administered for "as long as clinically indicated". The following are also stated in the labeling:

**"Dosages up to 90 mg b.i.d. have been administered".**

**"Daily Dosages greater than 20 mg should be administered in divided doses".**

Prevacid® sachets differ from Prevacid®capsules in that they contain inactive granules in addition to lansoprazole granules whereas Prevacid®capsules contain only active lansoprazole granules.

In this amendment, the sponsor provides responses on the information request contained in the Agency's letter dated November 21, 2000 (see Attachment I).

## II. REVIEW OF SPONSORS RESPENSE

**Comment 1**: In Comment 1, the sponsor was requested to provide complete acid resistance data as well as tabulated and graphical drug release profile for each dose unit of Prevacid® sachet for suspension tested for acid resistance and drug release, for which results were summarized in the bioequivalence study submitted in the original NDA.

The sponsor has submitted the requested information (see Attachment I [pages 4-8]). The information submitted by the sponsor is considered acceptable.

**Comment 2**: In Comment 2, the sponsor was requested to justify the use of [redacted] for drug release testing of Prevacid® sachet for suspension versus [redacted] for drug release testing of Prevacid® capsules as noted in the original NDA.

The sponsor submits the following lansoprazole release testing results for [redacted] for lansoprazole sachet for suspension (lansoprezole granules plus inactive granules [30 mg]) and at [redacted] or lansoprazole granules alone (30 mg).

| Product Analyzed | Paddle Speed (rpm) | Medium pH | Mean (SD) % Drug Release at Each Time-point (min) | | | | n |
|---|---|---|---|---|---|---|---|
| | | | 15 | 30 | 45 | 60 | |
| Lansoprazole Granules Alone | [redacted] | [redacted] | 84 (1.2) | 93 (1.8) | 96 (1.0) | 99 (0.9) | 6 |
| Lansoprazole Granules Alone | [redacted] | [redacted] | 76 (1.3) | 93 (1.2) | 95 (1.5) | 96 (1.2) | 6 |
| Lansoprazole Granules Plus Inactive Granules | [redacted] | [redacted] | 59 (4.3) | 89 (7.5) | 96 (3.7) | 97 (2.8) | 3 |

Based on these data, from the 30 min time-point, lansoprazole release profiles from lansoprazole granules alone were similar for the [redacted] Lansoprazole release from lansoprazole sachet for suspension (lansoprazole plus inactive granules) for the [redacted] appeared to be lower at the 15 and 30 min time-points. However, from the 45 min time-point, its release profile was similar to those of lansoprazole granules alone for the [redacted] or [redacted]. The sponsor states that the lower dissolution rate of lansoprazole sachet for suspension (versus lansoprazole granules alone) at the earlier drug release testing time points, in the dissolution medium with a pH value of [redacted] is related to increased medium viscosity caused by the components of the inactive granules.

Based on these findings, the sponsor feels that the use of [redacted] as an *in vitro* quality control tool for the assessment of lansoprazole release from lansoprazole sachet for suspension, is appropriate.

Data for *in vitro* dissolution testing of Prevacid® sachet using [redacted] and a temperature of 37±0.5°C is requested from the sponsor (see Overall Comment).

## OVERALL COMMENT

[redacted]

## RECOMMENDATION

Amendment 004 submitted to NDA 21-281 for lansoprazole (Prevacid®) 15 mg and 30 mg sachets for suspension on November 30, 200 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The data provided by the sponsor, related to acid resistance and drug release testing of Prevacid® 15 mg and 30 mg sachets for suspension submitted in the original NDA, are considered acceptable. However, the sponsor's justification for the use of _____ for the drug release testing of Prevacid® 15 mg and 30 mg sachets for suspension versus _____ for the drug release testing of Prevacid® 15 mg and 30 mg capsules is considered not acceptable. The sponsor needs to satisfactorily address the issues raised in the Overall Comment above prior to NDA approval.

Please convey this Recommendation and the Overall Comment above, as appropriate, to the sponsor.

/S/ 12/20/00

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. /S/ 12/20/00

cc: NDA 21-281, HFD-180, HFD-180 (Perry), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

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# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-281 SUBMISSION DATE: 06/30/00

LANSOPRAZOLE 15 MG AND 30 MG
SACHETS FOR SUSPENSION
PREVACID® SACHETS FOR SUSPENSION

TAP PHARMACEUTICAL PRODUCTS, INC.
LAKE FOREST, IL 60045 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: ORIGINAL NDA SUBMISSION CODE: 3S

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CONTENT PAGE



## I. SYNOPSIS/BACKGROUND

***What is the Drug?*** This NDA is submitted for lansoprazole (Prevacid®) 15 mg and 30 mg sachets for suspension.

***What Do We Know about Lansoprazole Drug Products***: Lansoprazole (Prevacid®) 15 mg and 30 mg capsules are approved drug products for the same indications as proposed for Prevacid® 15 mg and 30 mg sachets for suspension (see indications below). Prevacid® sachets differ from Prevacid®capsules in that they contain inactive granules in addition to the lansoprazole granules (see Drug Product Composition [page 2] for components of the inactive granules).

***What are the Proposed Indications and Dosages of Prevacid® 15 mg and 30 mg Satchet?***
The proposed indications and dosages of Prevacid® 15 mg and 30 mg Satchet are as follows:

**Short Term (up to Four Weeks) Treatment of Duodenal Ulcer in Adults**: 15 mg once daily.

***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Reoccurrence in Adults**
**(a) Tripple Therapy with Amoxicillin and Clarithromycin**: 30 mg Prevacid®, 1 g amoxicillin and 500 mg clarithromycin every 12 h for 10-14 days.
**(b) Dual Therapy with Amoxicillin**: 30 mg Prevacid®, 1 g amoxicillin every 8 h for 14 days

**Maintenance of Healed Duodenal Ulcers in Adults:** 15 mg every 24 h.

**Short Term (up to Eight Weeks) Treatment of Gastric Ulcers in Adults**: 30 mg every 24 h

**Short Term (up to Eight Weeks) Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD) in Adults**: 15 mg every 24 h.

**Short Term (up to Eight Weeks) Treatment of Erosive Esophagitis in Adults**: 30 mg every 24 h.

**Maintenance of Healing of Erosive Esophagitis in Adults:** 15 mg every 24 h.

**Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome in Adults:**
**Recommended Dosage**: 60 mg every 24 h (adjusted to individual patient needs and administered for "as long as clinically indicated". The following are also stated in the labeling:
**"Dosages up to 90 mg b.i.d. have been administered".**
**"Daily Dosages greater than 20 mg should be administered in divided doses".**

***What are the Compositions of Prevacid® 15 mg and 30 mg Satchet?*** The compositions of Prevacid® 15 mg and 30 mg sachets are stated in the NDA is presented in Table 1.

Table 1. The Composition of the Proposed Market Formulation of Prevacid® 15 mg and 30 mg Sachets

| Components | Compendial Status | Function | Amount per 15 mg sachet (g) | Amount per 30 mg sachet (g) |
|---|---|---|---|---|
| LANSOPRAZOLE GRANULES[a] | Non-Compendial | Active | 0.185[b] | 0.370[b] |
| INACTIVE GRANULES COMPOSED OF: | | | | |
| Confectioner's Sugar | NF | | | |
| Docusate Sodium | USP | | | |
| Ferric Oxide (Red Iron Oxide 62050) | NF | | | |
| Colloidal Silicon Dioxide | NF | | | |
| Mannitol (Granular 2080 LF[d]) | USP | | | |
| Xanthan Gum | NF | | | |
| Crospovidone | NF | | | |
| Citric Acid Monohydrate | USP | | | |
| Sodium Citrate Dihydrate | USP | | | |
| Magnesium Stearate | NF | | | |
| Trusil Artificial Strawberry Flavor Windsor 2373031 (K[e]) | Non-Compendial | | | |
| TOTAL | | | 5.585[b] | 5.77[b] |

[a]Lansoprazole granules include active and inactive ingredients as described in NDA 20-406
[b]Based on 100 percent potency of lansoprazole granules
[illegible] is used for granulation of a blend of confectioner's sugar and docusate sodium. The [illegible] is removed during granulation and is present in trace amounts in the inactive granules
[d]LF = low fines
[e]K = Kosher grade

***What is the Mechanism of Drug Action?*** Lansoprazole acts by non- competitive inhibition of the (H+,K+)-ATPase enzyme system (proton [acid] pump) at the secretory surface of the gastric parietal cell, thereby blocking the final step in the gastric acid secretion process.

***Why is this NDA Submitted when the 15 mg and 30 mg Lansoprazole Capsules that Are Approved for the above Indications Are Currently on the Market?*** The 15 mg and 30 mg Prevacid® Sachets are proposed for administration to patients who have difficulties swallowing capsules. The contents of the sachet is emptied into two tablespoonfuls of water in a suitable container, stirred well and administered immediately to the patient.

***What is the Purpose of this NDA Submission?*** The purpose of this NDA is to establish 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.

***What is the Nature of the Bioeqiuvalence Studies Submitted in the NDA?*** 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 and Prevacid® Delayed-Release capsule), conducted by the sponsor, are submitted in this NDA.

***Is Adequate Information Provided on the Methods of Sample Analysis?*** A satisfactorily validated liquid chromatography/mass spectrometry (LC/MS/MS) method was used in the bioequivalence studies.

***Is Adequate Information Provided on Acid Resistance and Dissolution of Lansoprazole Granules from the 15 mg and the 30 mg Prevacid® Sachet?*** The information provided on acid resistance and dissolution profiles of the lansoprazole granules from the 15 mg and 30 mg Prevacid® sachets is considered incomplete. Additional information is requested from the sponsor to assess the adequacy of the submitted drug release test methods and specifications.

***Is Adequate Food Effect Information Provided on Prevacid® Sachet?*** 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 is not necessary.

***Summary of Bioequivalence Study***: 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 are, respectively, bioequivalent to the currently marketed formulations of the 15 mg and 30 mg Prevacid® delayed-release capsules.

***How do the Adverse Event Profile of the 15 mg and the 30 mg Prevacid® Sachets Compare to those of the*** 15 mg ***Prevacid® Delayed-release Capsules in the Bioequivalence Studies (Protocols M98-944 and M98-945)?*** 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.

***What is the Recommendation***? The submitted bioequivalence data are deemed acceptable for consideration in the NDA approval process.

## II. SUMMARY OF INFORMATION ON PHARMACOKINETICS AND BIOEQUIVALENCE

### 1. *Is Adequate Pharmacokinetic Information Provided?*

The pharmacokinetic characteristics of lansoprazole were evaluated for the proposed market 15 mg Prevacid® sachet and the currently marketed 15 mg delayed-release Prevacid® capsule in 36 healthy subjects (Protocol M98-944) and for the proposed market 30 mg Prevacid® sachet and the currently marketed 30 mg delayed-release Prevacid® capsule in 36 healthy subjects (Protocol M98-945). Protocols M98-944 and M98-945 were Phase I, single dose, fasting, open label, randomized, two-period crossover studies. In each study, each subject received two single dose treatments (Treatment A [Test]: Prevacid® sachet formulation and Treatment B [Reference]: Prevacid® delayed-release capsule). In Treatment A, lansoprazole granules in the Prevacid® sachet was administered orally in a total of 180 mL of water (30 mL for preparing the granule suspension, 30 mL for cup rinsing and 120 mL as additional drinking water). In Treatment B, the intact Prevacid® delayed-release capsule was administered orally with 180 mL of water. In each study, the washout period between the two treatments was seven days.

The mean semi-logarithmic plots of lansoprazole plasma concentration versus time for Protocols M98-944 and M98-945 are presented in Figs. 1 and 2, respectively. The pharmacokinetic parameters of lansoprazole for Protocols M98-944 and M98-945 are summarized in Table 2. Individual subject pharmacokinetic parameters are presented in Appendix I (pages 12-19).

Fig. 1 Mean Plot of Lansoprazole Plasma Concentration Versus Time in Thirty-six Healthy Subjects Following a Single dose of 15 mg Lansoprazole as Capsule or as Sachet

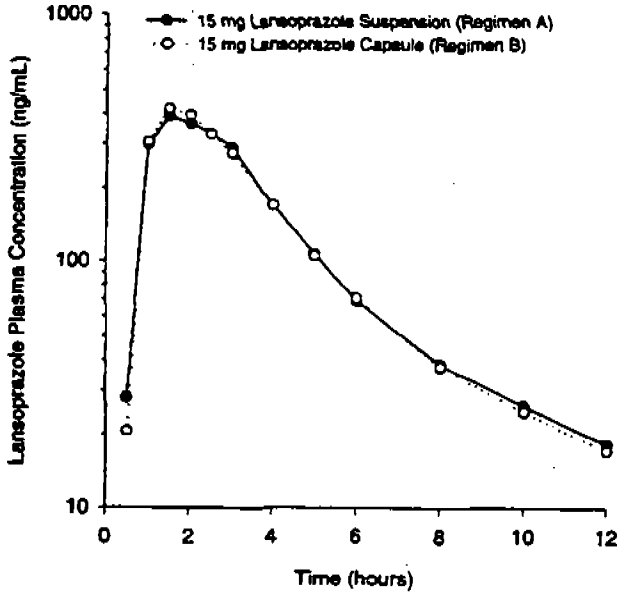

Fig. 2. Mean Plot of Lansoprazole Plasma Concentration in Thirty-six Healthy Subjects Following a Single 30 mg Dose of Lansoprazole as Capsule or as Sachet

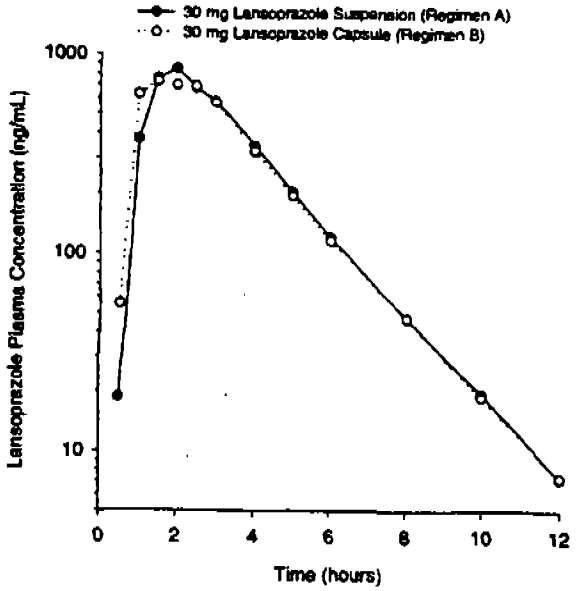


Table 2. Mean (SD) Pharmacokinetic Parameters in Healthy Subjects Following Single, 15 and 30 mg Doses of Lansoprazole Administered as Capsule or as Sachet.

| | n | Dose (mg) | $t_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_{infinity}$ (ng/ml*h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| Regimen A (Sachet) | 36 | 15 | 1.7 (0.8) | 591.9 (242.3) | 1614 (2065) | 1.05 (0.34) |
| Regimen B (Capsule) | 36 | 15 | 1.7 (0.8) | 578.6 (275.2) | 1620 (2290) | 1.03 (0.33) |
| Regimen A (Sachet) | 36 | 30 | 2.0 (0.7) | 1103 (428.3) | 2655 (1338) | 1.15 (0.32) |
| Regimen B (Capsule) | 36 | 30 | 1.8 (0.8) | 1077 465.6 | 2669 (1311) | 1.15 (0.32) |

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 are similar for the sachet and capsule formulations of lansoprazole.

## 2. *Is the Bioequvalence of Lansoprazole Administered as Sachet or as Capsule Adequately Evaluated?*

The bioequivalence of the proposed sachet formulations (Treatment A [Test]) and the currently marketed capsule formulations (Treatment B [Reference]) of the 15 mg and 30 mg doses of lansoprazole was evaluated in 36 healthy subjects (per dose) in the crossover studies described in item 1 above (Protocols M98-944 and M98-945). The Two One-sided t-test procedure, at the 90% confidence level, was used for bioequivalence assessment based on log-transformed $AUC_{infinity}$ and $C_{max}$. The results are summarized in Table 3.

Table 3. Bioequivalence of Lansoprazole in Twenty-six Healthy Subjects Following Administration of Single 15 mg and 30 Doses as Sachet and as Capsule

| Geometric Mean[a] | Dose (mg) | Treatment A (Sachet) | Treatment B (Capsule) | A/B (%) | 90% C.I[b] (%) |
|---|---|---|---|---|---|
| $AUC_{infinity}$ (ng/mL*h) | 15 | 1191 | 1145 | 104.0 | 94.9-117.9 |
| $C_{max}$ (ng/mL) | 15 | 555.2 | 524.9 | 105.8 | 95.9-112.8 |
| $AUC_{infinity}$ (ng/mL*h) | 30 | 2356 | 2340 | 100.7 | 91.4-110.9 |
| $C_{max}$ (ng/mL) | 30 | 1022 | 972.2 | 105.1 | 93.0-118.8 |

[a]Least square mean, [b]Confidence interval

The 90% confidence intervals for log-transformed $AUC_{infinity}$ ($AUC_{inf}$) and $C_{max}$ (94.9-117.9% and 95.9-112.8%, respectively, for the 15 mg dose and 91.4-110.9% and 93.0-118.8%, respectively, for the 30 mg dose) were within the range of required for bioequivalence. Based on these findings, the proposed sachet 15 mg and 30 mg sachet formulations of lansoprazole are, respectively, bioequivalent to the currently marketed 15 mg and 30 mg delayed release capsule formulations.

## 3. *Is Adequate Information Provided on Drug Product Dissolution?*

The dissolution Method and Specifications for the acid resistance and drug release provided in the NDA are presented in Table 4.

Table 4. Acid Resistance and Dissolution Testing Methods and Specifications for 15 mg and 30 mg Lansoprazole Sachets and the Currently Marketed 15 mg and 30 mg Lansoprazole Delayed-release Capsules

**Acid Resistance**

| | Lansoprazole Suspension (Sachet) | Lansoprazole Capsule |
|---|---|---|
| Apparatus: | | |
| Paddle Speed: | | |
| Medium: | | |
| Sampling Time: | | |
| Analysis: | | |
| Specification: | | |

**Drug Release**

| | Lansoprazole Suspension (Sachet) | Lansoprazole Capsule |
|---|---|---|
| Apparatus: | | |
| Paddle Speed: | | |
| Medium: | | |
| Sampling Time: | | |
| Analysis: | | |
| Specification: | | |

The drug release methods for the sachet and the capsule formulations differ in dissolution media, media pH and paddle speeds. In the NDA, it is stated that the above dissolution specifications are based on the data summarized in Tables 5 and 6.

Table 5. Summary of Acid Resistance for 15 mg and 30 mg Lansoprazole Sachet (Suspension) in maintained at pH of and Temperature of

| Dose (mg) | Batch Size | Mean Percentage (%RSD) Drug Release Profile (n=12 for each medium) | | | | |
|---|---|---|---|---|---|---|
| | | % Release in Acid in 2 h | % Release in | | | |
| | | | 15 min | 30 min | 45 min | 60 min |
| 15 | | 0.52 | 65 (8.2) | 86 (5.7) | 93 (3.1) | 96 (2.4) |
| 30 | | 0.72 | 55 (9.6) | 88 (4.2) | 95 (1.9) | 97 (2.6) |

Table 6. Summary of Acid Resistance for 15 mg and 30 mg Lansoprazole Capsule in 500 mL 0.1N HCl and Drug Release in 900 mL Phosphate Buffer, with SDS, maintained at pH of 6.8 and Temperature of 37±0.5°C

| Dose (mg) | Batch Size (Dose units) | Individual Dose Unit Drug Release (n=6 for each Medium) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | % Released in Acid in 2 h | | | | | | % Release in in 60 min | | | | | |
| 15 | | 2 | 2 | 2 | 3 | 3 | 2 | 102 | 113 | 106 | 103 | 98 | 107 |
| 30 | | 2 | 2 | 2 | 2 | 2 | 2 | 109 | 110 | 110 | 105 | 111 | 106 |

For each dose unit of the sachet and capsule tested, the sponsor is requested to provide complete tabulated acid resistance drug release data. The sponsor is further requested to justify the use of [redacted] for drug release testing of the sachet formulation versus [redacted] and a pH value of [redacted] for the capsule formulations (see Overall Comment [page 10]).

4. ***Is Adequate Information Provided on Sample Analytical Methods?***

The plasma samples in the bioequivalence studies (Protocols M98-944 and M98-945) were analyzed using adequately validated LC/MS/MS methods. The following assay validation information is provided for both studies:

**Limit of Quantification**: [redacted]

**Linearity Range**: [redacted]

**Precision and Accuracy**

| Concentration (ng/mL) | | 15.0 | 100 | 900 |
|---|---|---|---|---|
| Precision (%CV): | Within Day: | 7.2 | 5.2 | 4.5 |
| n: | | 6 | 6 | 6 |
| | Between Day: | 5.0 | 4.7 | 4.0 |
| n: | | 18 | 18 | 18 |
| Accuracy (%): | Within Day: | 102.9 | 106.8 | 101.8 |
| n: | | 6 | 6 | 6 |
| Accuracy (%): | Between Day: | 100.6 | 103.4 | 99.3 |
| n: | | 18 | 18 | 18 |

**Specificity**: Lansoprazole eluted from plasma samples without significant interference by endogenous substances.

**Stability**: The following information is provided in the NDA on lansoprazole stability.

**(a) Analysis of Plasma Samples**

**(i) Long Term Stability (Storage Temperature of -20°C for $\geq$11 months)**

| Concentration (ng/mL): | 15.0 | 100.0 | 900.0 |
|---|---|---|---|
| Initial Analysis | | | |
| Recovery (%): | 98.7 | 101.0 | 94.1 |
| CV(%): | 2.2 | 2.8 | 1.2 |
| n: | 6 | | 6 |
| Reanalysis | | | |
| Recovery (%): | 106.7 | 107.0 | 107.3 |
| CV(%): | 7.1 | 3.1 | 2.3 |
| n: | 6 | | 6 |

### (ii) Bench Top Stability at Ambient Temperature for 98 h

| Concentration (ng/mL): | 15.0 | | 100.0 | | 1500.0 | |
|---|---|---|---|---|---|---|
| Time of Analysis (h) | 0 | 98 | 0 | 98 | 0 | 98 |
| Recovery (%): | 103.3 | 98.0 | 106.0 | 102.0 | 103.0 | 103.7 |
| CV(%): | 6.4 | 4.7 | 3.4 | 8.3 | 3.0 | 3.3 |
| n: | 6 | 5 | 6 | 6 | 6 | 6 |

### (iii) Freeze-thaw Stability for Three Freeze-thaw Cycles

| Concentration (ng/mL): | 15.0 | | | 100.0 | | | 1500.0 | | |
|---|---|---|---|---|---|---|---|---|---|
| Freeze/thaw Cycle: | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| Recovery (%): | 97.3 | 88.7 | 89.3 | 101 | 93.7 | 96.1 | 87.0 | 83.2 | 87.1 |
| CV(%): | 10.8 | 7.0 | 4.0 | 9.8 | 3.0 | 5.1 | 4.1 | 2.3 | 4.0 |
| n: | 6 | 6 | 6 | 9.8 | 3.0 | 5.1 | 6 | 6 | 6 |

The freeze-thaw stability data suggest that in the lansoprazole plasma concentrations range of [redacted] the accuracy of the assay (recovery of lansoprazole from plasma sample) may be reasonably reduced in a second or third freeze/thaw cycle. However, there is no evidence in the NDA suggesting that freeze-thaw processes were involved in the plasma sample analysis in the bioequivalence studies (Protocols M98-944 and M98-945). Accordingly, the submitted assay validation information is acceptable.



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## III. OVERALL COMMENT

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. Additionally, please justify the use of [redacted] for drug release testing of the Prevacid® sachet formulations versus [redacted] and a pH value of [redacted] for the Prevacid® capsule formulations.

## IV. RECOMMENDATION

NDA 21-281 submitted for lansoprazole (Prevacid®) 15 mg and 30 mg sachets for suspension, by the sponsor, on June 30, 2000 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. 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. Accordingly, the sponsor's revision of 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® sachets for suspension, is considered acceptable. The sponsor's revision of the clinical pharmacology related statements in other sections of this labeling to include the 15 mg and 30 mg Prevacid® sachets for suspension is also considered acceptable.

This Recommendation is contingent upon a satisfactory report of the DSI Inspection that was ordered by the Agency in connection with this NDA. Furthermore, the issues raised in the Overall Comment above need to be satisfactorily addressed by the sponsor prior to NDA approval.

Please convey this Recommendation and the Overall Comment above, as appropriate, to the sponsor.

/S/ 11/03/00

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

Concurrence: Suresh Doddapaneni, Ph.D. /S/ 11/7/00

Clinpharm/Biopharm Briefing: 10/31/00 at 11.30 a.m. (Attendees: HFD-870: Malinowski, Hunt, Doddapaneni; HFD-180: Kress).

cc: NDA 21-281, HFD-180, HFD-180 (Perry), HFD-870 (Malinowski, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).