CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-327

MEDICAL REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH
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MEMORANDUM

Date: May 18, 2009

From: Joel Schiffenbauer, M.D.
Deputy Director, DNCE

Subject: NDA 22-327/Prevacid

Sponsor: Novartis

This memorandum will document required labeling changes to the Prevacid label that was approved on May 13, 2009 for OTC use. That approved labeling contains the following language [redacted] b(4)

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/s/

Joel Schiffenbauer
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-327
Priority or Standard	Standard
Submit Date(s)	July 15, 2008
Received Date(s)	July 16, 2008
PDUFA Goal Date	May 15, 2009
Reviewer Name(s)	Ali Niak, M.D.
Review Completion Date	April 13, 2009
Established Name	Lansoprazole
(Proposed) Trade Name	Prevacid 24HR
Therapeutic Class	Proton Pump Inhibitor
Applicant	Novartis Consumer Health, Inc.
Formulation(s)	Delayed-Release Capsules
Dosing Regimen	15 mg once a day for 14 days (14-day course may be repeated every 4 months)
Indication(s)	Treatment of frequent heartburn (occurs 2 or more days per week)
Intended Population(s)	Adults (≥ 18 years old)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical efficacy standpoint, this reviewer recommends that lansoprazole delayed release capsules (15 mg) for over the counter (OTC) use be approved at a dose of 15 mg per day for 14 days for the relief of frequent heartburn occurring two or more days a week pending revisions to the proposed labeling. The information in this submission provides substantial evidence to support the proposed indication, and there are data to provide adequate directions for use.

This reviewer's recommendation is contingent upon the findings of other reviewers that include the clinical reviewer from the Office of Non-Prescription Products (ONP), the statistics reviewer from the Office of Biostatistics (OB), the clinical pharmacology reviewer from the Office of Clinical Pharmacology (OCP), and the chemistry reviewer from the Office of New Drug Quality Assessment (ONDQA).

1.2 Risk Benefit Assessment

Lansoprazole 15 mg has been prescribed by physicians in the United States since 1995. There is extensive efficacy data for lansoprazole for the treatment of heartburn in NDA 20-406 for prescription lansoprazole. In addition, the efficacy results in this submission demonstrate the efficacy of lansoprazole 15 mg for the treatment of frequent heartburn (occurring two or more days a week for two weeks) in adults ($\geq$ 18 years of age); treatment is for 14 days and a 14-day course may be repeated (if needed) every 4 months. There were no major safety signals [see review performed by Dr. Lolita Lopez in the Division of Nonprescription Clinical Evaluation (DNCE) under the same NDA (NDA 22-327)]. Therefore, given the combined evidence of effectiveness for the treatment of heartburn and the lack of new safety signals detected, the use of lansoprazole for OTC use over a 14-day course is warranted.

1.3 Recommendations for Postmarket Risk Management Activities

No post-market risk management activities are recommended for this NDA.

1.4 Recommendations for Postmarket Studies/Clinical Trials

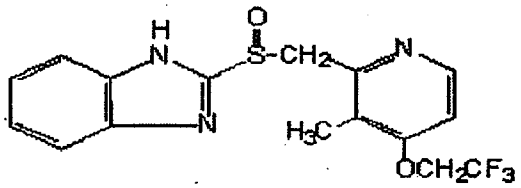
No post-market studies or clinical trials are recommended for this NDA.

2 Introduction and Regulatory Background

2.1 Product Information

Prevacid (lansoprazole) belongs to a class of antisecretory compounds that do not exhibit anticholinergic or H_2-RA properties, but that suppress gastric acid secretion by specific inhibition of the (H+/K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Since this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

The active ingredient in Prevacid (lansoprazole) is a substituted benzidimazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzidimazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_3S$ with a molecular weight of 369.37. The structural formula is:



Prevacid (lansoprazole) was approved in the U.S. for use in adults in May 1995, for use in children 1 to 11 years of age in June 2002 and for use in adolescents 12 to 17 years of age in June 2004. Lansoprazole has approved indications for adults that include the short-term treatment of symptomatic, non-erosive GERD (15 mg once daily [QD] up to 8 weeks), the short-term treatment of erosive esophagitis (EE) (30 mg per day up to 8 weeks; patients with unhealed EE after 8 weeks of treatment [5%-10%] may benefit from an additional 8 weeks of treatment), the long term maintenance of healed EE (30 mg once a day), short-term treatment and maintenance of healed duodenal ulcers (15 mg once a day), short-term treatment of gastroesophageal ulcers, healing and risk reduction of nonsteroidal anti-inflammatory drug (NSAID)-associated gastroesophageal ulcers (15 mg once a day for up to 8 weeks), and for the treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome (60 mg once a day).

The proposed indication for lansoprazole delayed-release capsules, (15 mg per capsule) is the treatment of frequent heartburn (occurring 2 or more days a week) in adults 18 years of age and older. Lansoprazole delayed-release capsules contain the active ingredient lansoprazole in a two piece hard gelatin capsule with a black tamper-evident band for oral ingestion.

Heartburn can occur when acidic stomach contents move into the esophagus from the stomach, thereby, causing a burning sensation in the chest or throat. Acid production in the stomach is stimulated when gastrin, acetylcholine, or histamine bind to their respective receptors on the gastric parietal cell and induce the hydrogen/potassium ion adenosine triphosphatase proton pump (H^+/K^+-ATPase) to release H^+ ions by replacing it with K^+. Most heartburn sufferers have events occurring both during the day and at night.

2.2 Currently Available Treatments for Proposed Indications

Currently, the medical treatment for the OTC indication of frequent heartburn includes another proton pump inhibitor (PPI), omeprazole, available as omeprazole magnesium (Prilosec OTC) and omeprazole delayed release tablets. Omeprazole OTC is presently marketed for use in adults ($\geq$ 18 years old) for frequent heartburn once a day for 14 days and can be repeated every 4 months if needed.

Other classes of OTC medications that are available for the treatment of frequent heartburn include H_2-receptor antagonists such as ranitidine and cimetidine, and antacids such as aluminum hydroxide and calcium bicarbonate.

2.3 Availability of Proposed Active Ingredient in the United States

Prevacid is the only product (by prescription) containing lansoprazole that is available in the United States. Orally, it is available in the 15 mg and 30 mg strengths in capsule form, oral suspension (unit dose packaging), and orally disintegrating tablets. Additionally, an injectable form of lansoprazole is available in the 30 mg strength dosage.

2.4 Important Safety Issues With Consideration to Related Drugs

Atazanavir is an HIV protease inhibitor whose absorption is dependent upon the presence of gastric acid. Since lansoprazole causes long-lasting inhibition of gastric acid secretion, it substantially decreases the systemic concentrations of atazanavir. As a result of lansoprazole, this decreased absorption can result in a loss of therapeutic effect of atazanavir and the possible development of HIV resistance.

Theophylline is metabolized through the cytochrome P450 system, specifically through the CYP1A2 and CYP3A isoenzymes. When lansoprazole was administered concomitantly with theophylline, there was a 10% increase in the clearance of theophylline. Although this interaction is not likely to be of clinical concern, nevertheless, patients may require additional titration of their theophylline dosage when taking lansoprazole concurrently in order to ensure clinically effective levels in blood.

There have been reports of increased International Normalized Ratio (INR) and Prothrombin Time (PT) in patients who are on warfarin and PPI's (including lansoprazole) concomitantly. Patients who are on warfarin and are being treated by a PPI, concomitantly, may need to be monitored for changes in the INR and PT in order to prevent abnormal hemorrhage or death.

Lansoprazole (CYP2C19, CYP3A4 substrate) may potentially inhibit CYP3A4-mediated metabolism of tacrolimus, and thereby, substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers.

Drug-drug interactions are discussed in greater detail in Section 4.4.3 of this review. For a full review of safety, please refer to the review performed by Dr. Lolita Lopez in the Division of Nonprescription Clinical Evaluation (DNCE) under the same NDA (NDA 22-327).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The availability of Prevacid (lansoprazole; Takeda Abbott Pharmaceuticals [TAP]) in the United States is as follows:

- On May 10, 1995, the FDA approved Prevacid® (lansoprazole) Delayed-Release Capsules for the treatment of gastrointestinal acid-related disorders in adults (NDA 20-406)
- On May 3, 2001, Prevacid® (lansoprazole) Delayed-Release Oral Suspension was approved (NDA 21-281)
- On August 30, 2002, Prevacid® SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablets was approved (NDA 21-428)

Currently, lansoprazole is approved for the management of duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), erosive esophagitis, and pathological hypersecretory conditions. However, no OTC indications exist for lansoprazole in the United States. TAP Pharmaceutical Products holds the rights to NDA 20-406 and IND 30,159 and has granted the Applicant, Novartis Consumer Health, Inc. (NCH) right of reference to that data to support the current application (NDA 22-327) for Prevacid® for OTC use.

On April 6, 2006, a pre-IND meeting was held between NCH and the FDA in order to discuss the proposal for the OTC indication and its design. IND 74,256 was initiated on May 5, 2006, by NCH for OTC use of lansoprazole delayed-release capsules. On July 27, 2006, a Special Protocol Assessment (SPA) was requested by NCH for study 305. The SPA for Study 305 listed several conclusions and recommendations which are noteworthy. The daily collection of the patient-reported outcomes (PROs) data in order to eliminate recall bias, was acceptable and did conform to the May 2002 Special Protocol Assessment Guidance. It was recommended that the study population should have baseline frequent nighttime heartburn (patients with ≥ 2 mean nighttime heartburn episodes per week). [

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] Please refer to DARRTS for

responses to the Applicant's questions (September 8, 2006). A pre-NDA meeting was held to discuss NCH plans to submit a 505(b)(1) NDA on March 17, 2008, for OTC use of Prevacid delayed-release capsules for the treatment of frequent heartburn, and on July 16, 2008, the FDA received the 505(b)(1) application requesting the OTC use of lansoprazole delayed-release capsules for frequent heartburn (NDA 22-327).

2.6 Other Relevant Background Information

Presently, lansoprazole is the only PPI in the U.S. that is approved for the indication of healing of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcers.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A Division of Scientific Investigations (DSI) inspection was requested for all three studies. The selection of sites was based on higher number of subjects enrolled per site and higher proportion in the treatment group meeting the primary endpoint than other sites. For Study 301, site number 124 was chosen, for Study 302, site number 215 was chosen, and for Study 305, site number 548 was chosen.

At the time of the writing of this review, the preliminary inspection results for Study 301 and the final results for Studies 302 and 305 were acceptable.

3.2 Compliance with Good Clinical Practices

The study was conducted in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP) guidelines, Food and Drug Administration (FDA) regulations, ethical principles that have their origin in the Declaration of Helsinki, and all applicable local regulations, whichever offered the greater protection for the subject. During the screening visit (Visit 1), each subject signed an informed consent statement. Additionally, a study coordinator and/or investigator addressed any questions that were raised by the subjects and information regarding the study was provided to the subjects.

3.3 Financial Disclosures

The Applicant certified that it did not enter into any financial agreement with the clinical investigators whereby the value of their compensation could be affected by outcome of the studies. None of the clinical investigators in any of the three studies reported significant equity in NCH as defined in 21 CFR 54.2(b).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The active substance for OTC Prevacid is lansoprazole (15 mg) and under NDA 20-406, this was approved for prescription use. Reference is made by NCH to NDA 20-406 for the CMC information. Please refer to the Chemistry review for further details, specifically to the review from March 25, 2009, by Dr. Yichun Sun.

4.2 Clinical Microbiology

A microbiology review was not necessary for this application.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology or toxicology data were submitted with this NDA. No requests were made by the FDA for any new preclinical studies either. The animal data and toxicology studies were referenced from NDA 20-406 that had already been submitted and approved by the FDA.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H_2-receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Due to the fact that this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

4.4.2 Pharmacodynamics

After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was greater than 3 and greater than 4.[1] Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated

[1] Physicians Desk Reference, 2009.

gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

After the initial dose, increased gastric pH was seen within 1-2 hours with 30 mg of lansoprazole and 2-3 hours with 15 mg of lansoprazole. After multiple daily dosing, increased gastric pH was seen within the first hour post-dosing with 30 mg of lansoprazole and within 1-2 hours post-dosing with 15 mg of lansoprazole.

The inhibition of gastric acid secretion as measured by intragastric pH gradually returned to normal over two to four days after multiple doses. There was no indication of rebound gastric acidity.

4.4.3 Pharmacokinetics

The absorption of lansoprazole is rapid, with the mean C_{max} occurring approximately 1.7 hours after oral dosing, and the absolute bioavailability is over 80%. In healthy subjects, the mean (±SD) plasma half-life was 1.5 (±1.0) hours. Both the C_{max} and AUC are diminished by about 50% to 70% if lansoprazole is given 30 minutes after food, compared to the fasting condition. There is no significant food effect if lansoprazole is given before meals.

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 μg/mL.

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by (H^+,K^+)-ATPase within the parietal cell canaliculus, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than two hours, while the acid inhibitory effect lasts more than 24 hours.

In one study, approximately 1/3 of the administered single dose of ^{14}C-lansoprazole was excreted in the urine and 2/3's was recovered in the feces. This implies that biliary excretion is a significant mode of excretion for lansoprazole. Lansoprazole does not accumulate and no alteration occurs in its pharmacokinetics (PK) by multiple dosing.

Drug-Drug Interactions:
Lansoprazole is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes. No clinically significant interactions have been shown in healthy subjects between lansoprazole and other drugs metabolized by the cytochrome P450 system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin.

Atazanavir is an HIV protease inhibitor whose absorption is dependent upon the presence of gastric acid. Since lansoprazole causes long-lasting inhibition of gastric acid secretion, it substantially decreases the systemic concentrations of atazanavir. As a result of lansoprazole, this decreased absorption can result in a loss of therapeutic effect of atazanavir and the possible development of HIV resistance.

Theophylline is metabolized through the cytochrome P450 system, specifically through the CYP1A2 and CYP3A isoenzymes. When lansoprazole was administered concomitantly with theophylline, there was a 10% increase in the clearance of theophylline. Although this interaction is not likely to be of clinical concern, nevertheless, patients may require additional titration of their theophylline dosage when taking lansoprazole concurrently in order to ensure clinically effective levels in blood.

There have been reports of increased International Normalized Ratio (INR) and Prothrombin Time (PT) in patients who are on warfarin and PPI's (including lansoprazole) concomitantly. Patients who are on warfarin and are being treated by a PPI, concomitantly, may need to be monitored for changes in the INR and PT in order to prevent abnormal hemorrhage or death.

A delay of the absorption of lansoprazole (30 mg) or omeprazole (20 mg) was noted in a single-dose crossover study when sucralfate (1 gm) was given concomitantly as compared to the administration of the PPI by itself; there was a 17% reduction in bioavailability in lansoprazole and 16% bioavailability reduction in omeprazole with concomitant administration of sucralfate. However, no evidence of a change in lansoprazole efficacy was noted in clinical trials when lansoprazole was administered concomitantly with antacids.

An interaction may exist between lansoprazole and tacrolimus. Lansoprazole (CYP2C19, CYP3A4 substrate) may potentially inhibit CYP3A4-mediated metabolism of tacrolimus, and thereby, substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers. (For a full explanation of the interaction between lansoprazole and tacrolimus, please refer to the review by Dr. Insook Kim in the Division of Clinical Pharmacology III for NDA's 20-406, 21-281, and 21-428.)

Geriatrics:
No dosage adjustment is necessary in the elderly.

Gender:
No gender differences have been found in PK and intragastric pH results.

Pediatrics:
The PK of lansoprazole were studied in pediatric patients with GERD ages 1 to 11 years and 12 to 17 years in separate clinical studies. In the 1 to 11 years age group, lansoprazole was dosed at 15 mg per day for subjects weighing $\leq$ 30 kg and at 30 mg per day for subjects weighing > 30 kg. Adolescent subjects between and including ages 12 to 17 were randomized to receive lansoprazole 15 or 30 mg per day. The PK of lansoprazole in the pediatric subjects ages 1 to 17

years of age were similar to the healthy adult subjects. According to the literature regarding the ontogenic development of 2C19 (Clin Pharmacokinet 2005; 44 (5):441 & Pediatr Clin North Am 1997; 44: 55-77), lansoprazole's activity is low in the first few weeks of life, reaches the adult level by 6-12 months of age, and then exceeds the adult level between 1 and 4 years old and then gradually declines to the adult level by puberty.

Renal Insufficiency:
The AUC for free lansoprazole in plasma has been shown not to be related to the degree of renal impairment in patients with severe renal insufficiency; the C_{max} and T_{max} are not different than subjects with normal renal function either. No dosage adjustment is necessary in patients with renal insufficiency.

Hepatic Insufficiency:
In patients with various degrees of chronic liver disease, the mean plasma half-life of lansoprazole was prolonged to 3.2-7.2 hours (from 1.5 hours). There was an increase in the mean AUC of up to 500% in patients with hepatic impairment compared to healthy subjects. Therefore, dose reduction in patients with severe hepatic disease should be considered.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The efficacy of lansoprazole 15 mg per day over a 14 day course for the treatment of frequent heartburn was evaluated. Three clinical efficacy studies were conducted by the Applicant (301, 302, and 305). A total of 1986 subjects enrolled in these placebo-controlled, randomized studies.

The primary efficacy endpoint in Studies 301 and 302 was the proportion of 24-hour days with no heartburn during 14 days of treatment with 15 mg of lansoprazole per day. The primary efficacy endpoint in Study 305 was the proportion of nighttimes with no heartburn during 14 days of treatment with 15 mg of lansoprazole per day. Additionally, on an exploratory basis, the efficacy of 30 mg of lansoprazole per day for 14 days for the treatment of frequent heartburn was investigated in Study 305.

A secondary efficacy endpoint in Studies 301 and 302 was the proportion of 24-hour days with no heartburn over Days 1 through 2. Furthermore, a secondary efficacy endpoint in all 3 studies was the proportion of subjects with no heartburn during Day 1.

The tertiary efficacy endpoint in Study 305 was also the proportion of 24-hour days with no heartburn over Days 1 through 2.

Table 1: Overview of Phase III Clinical Studies

Parameters	Study 301	Study 302	Study 305
No. Trial Sites	35 (U.S.)	37 (U.S.)	61 (U.S.)
No. Subjects	N=564	N=570	N=852
Objective	Efficacy/Safety in subjects with frequent heartburn	Efficacy/Safety in subjects with frequent heartburn	Efficacy/Safety in subjects with frequent heartburn
Trial Design	Multicenter, double-blind, randomized, parallel group, placebo-controlled study in a population of frequent heartburn sufferers ≥ 2 episodes per week	Multicenter, double-blind, randomized, parallel group, placebo-controlled study in a population of frequent heartburn sufferers ≥ 2 episodes per week	Multicenter, double-blind, randomized, parallel group, placebo-controlled study in a population of frequent heartburn sufferers ≥ 2 episodes per week at nighttime
Treatment	Randomized 1:1 to Lansoprazole 15 mg or Placebo (orally before breakfast) ↓ 7 day Placebo Run-in period ↓ 14 day Active/Placebo-controlled treatment period ↓ 7 day Placebo follow-up period	Randomized 1:1 to Lansoprazole 15 mg or Placebo (orally before breakfast) ↓ 7 day Placebo Run-in period ↓ 14 day Active/Placebo-controlled treatment period ↓ 7 day Placebo follow-up Period	Randomized 1:1 to Lansoprazole 15 mg or 30 mg or Placebo (orally before breakfast) ↓ 7 day Placebo Run-in period ↓ 14 day Active/Placebo-controlled treatment period ↓ 7 day Placebo follow-up period
Efficacy Endpoints	▪ *Primary:* proportion of days with no heartburn over 14 days ▪ *Secondary:* (a) proportion of nighttimes with no heartburn over 14 days; (b) proportion of days with no heartburn over Days 1-2; (c) proportion of subjects w/ no heartburn on Day 1	▪ *Primary:* proportion of days with no heartburn over 14 days ▪ *Secondary:* (a) proportion of nighttimes with no heartburn over 14 days; (b) proportion of days with no heartburn over Days 1-2; (c) proportion of subjects w/ no heartburn on Day 1	▪ *Primary:* proportion of nighttimes with no heartburn over 14 days ▪ *Secondary:* (a) proportion of 24-hr. days with no heartburn over 14 days; (b) proportion of subjects w/ no heartburn on Day 1 ▪ *Tertiary:* proportion of 24-hour days with no heartburn over Days 1-2

(Table above compiled by this reviewer from Study Reports, Clinical Overview, and Efficacy Summary.)

5.2 Review Strategy

This review will evaluate the efficacy of lansoprazole 15 mg for OTC use by reviewing the efficacy data obtained through the three trials as submitted by the Applicant. Dr. Freda Cooner reviewed the statistical aspects of the NDA. The review of safety information in this NDA is in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Products (ONP).

5.3 Discussion of Individual Studies/Clinical Trials

There were three phase III, multicenter (U.S. sites), randomized, double-blind, placebo-controlled, parallel group studies comprising a total of 1986 subjects. The three studies (301, 302, and 305) are outlined in Table 1 (please refer to Section 5.1).

6 Review of Efficacy

The clinical development program of lansoprazole 15 mg for short-term OTC use consisted of three Phase III placebo-controlled trials in subjects with frequent heartburn.

The design and objectives of two of the studies, 301 and 302, were identical. The primary objective of these two studies was to demonstrate that lansoprazole 15 mg once daily dosed in the morning is superior to placebo in reducing the frequency of heartburn episodes during the 14-day double-blind treatment period. The study cohorts consisted of subjects with a history of frequent heartburn, regardless of when their symptoms occurred (during the day or nighttime).

The third study, 305, was also conducted in a population of frequent heartburn sufferers utilizing the same study design employed in Studies 301 and 302. However, all subjects in Study 305 were also required to have a history of frequent heartburn during the nighttimes, a requirement which was not stipulated in Studies 301 and 302. The primary objective of Study 305 was to demonstrate that lansoprazole 15 mg dosed once daily in the morning is superior to placebo in reducing the frequency of nighttime heartburn episodes during the 14-day double-blind treatment period.

6.1 Indication

The indication proposed in this NDA for OTC once a day lansoprazole delayed release capsule 15 mg is shown below.

- treats frequent heartburn (occurring 2 or more days a week for 14 days) in adults 18 years of age and older
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect
- the treatment course may be repeated every 4 months if necessary

6.1.1 Methods

The safety and efficacy of lansoprazole 15 mg for short-term OTC use was investigated in the target population (adults 18 years of age or older with a history of frequent heartburn) over a 14-day period. Three large, randomized, double-blind, placebo-controlled, parallel group, Phase III studies (301, 302 and 305) involving 1986 patients with frequent heartburn were conducted to support the current application; of these 1986 patients, 861 received lansoprazole 15 mg, 277 received lansoprazole 30 mg, and 848 received placebo for 14 consecutive days. Efficacy evaluation was based on the subject's daily self-assessment regarding the occurrence of heartburn episodes as well as the compliance of study medication use during the 14-day treatment period.

Studies 301, 302, and 305 were all multicenter, double-blind, randomized, controlled, 2- or 3-arm trials of identical general design (please refer to the figure below).

Subjects included in the studies had heartburn occurring on a minimum of 2 or more days a week over the past month if their heartburn was left untreated; in Study 305 only, subjects were required to have nighttime heartburn on at least 2 days per week over the past month.

Subjects with a history of erosive esophagitis verified by endoscopy, or gastroesophageal reflux disease diagnosed by a physician and confirmed by endoscopy, were excluded.

Subjects received lansoprazole 15 mg/day, placebo or, in Study 305 only, lansoprazole 30 mg/day.

Figure 1. General Study Design

← Screening →	← Run-in →	← Treatment →		← Follow-up →
Heartburn medication washout	Single-blind placebo	Randomization Start of double-blind treatment	End of double-blind treatment	Single-blind placebo follow-up
Day -14 (±2)	Day -8 (+4)	Day 1	Day 16 (+4)	Day 24 (+4)
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5

In all three studies, eligible subjects underwent a screening and heartburn medication washout period prior to entering the single-blind placebo run-in period, each one week in duration. Following the successful completion of the run-in period and having met all required entry criteria, subjects were randomized in equal ratio to receive the active or placebo treatments for 14 days during the double-blind treatment period, to be followed immediately by the 7-day single-blind placebo follow-up period. No dose adjustment during the double-blind treatment period was allowed.

The efficacy endpoints for Studies 301, 302, and 305 are summarized in the table below.

Study	Endpoint
301 and 302	Primary Endpoint: ▪ proportion of days with no heartburn over 14 days Secondary Endpoints: ▪ proportion of nighttimes with no heart-burn over 14 days ▪ proportion of days with no heartburn over Days 1-2 ▪ proportion of subjects with no heartburn on Day 1
305	Primary Endpoint: proportion of nighttimes with no heartburn over 14 days Secondary Endpoints: ▪ proportion of 24-hr. days with no heartburn over 14 days; ▪ proportion of subjects w/ no heartburn on Day 1 Tertiary Endpoint: ▪ proportion of 24-hour days with no heartburn over Days 1-2

For all 3 studies, the sample size estimate was based on 90% power to detect an approximate 15% treatment difference between the active and placebo groups. Statistical analyses for efficacy were performed individually for each of the three studies using the Intent-to-Treat (ITT) and per protocol populations. In addition, efficacy analyses for lansoprazole 15 mg were performed using the pooled data of the ITT populations from all 3 studies.

6.1.2 Demographics and Baseline Disease Characteristics

Demographics

Baseline demographic characteristics by treatment group and by study are summarized in the tables below.

Table 2. Demographic features by treatment group

	Lansoprazole 15 mg	Lansoprazole 30 mg	Placebo
Total subjects *	861	277	848
Gender - n (%)			
Male	320 (37.2)	94 (33.9)	295 (34.8)
Female	541 (62.8)	183 (66.1)	553 (65.2)
Race - n (%)			
Caucasian	609 (70.7)	191 (69.0)	587 (69.2)
Hispanic	117 (13.6)	35 (12.6)	123 (14.5)
Black	97 (11.3)	41 (14.8)	100 (11.8)
Asian	22 (2.6)	9 (3.2)	22 (2.6)
Other	16 (1.9)	1 (0.4)	16 (1.9)
Age (yr) - n (%)			
N	861	277	848
Mean ± SD	48.0 ± 14.2	48.8 ± 14.1	47.7 ± 13.6
Median	48.0	49.0	48.0
Range	18 - 90	18 - 85	18 – 86
< 40	238 (27.6)	67 (24.2)	239 (28.2)
40 - 65	518 (60.2)	172 (62.1)	505 (59.6)
≥ 65	105 (12.2)	38 (13.7)	104 (12.3)
Height (inches)			
N	861	277	847
Mean ± SD	66.1 ± 3.9	66.1 ± 4.2	66.0 ± 4.0
Median	66.0	65.0	65.0
Range	52 - 76	54 - 78	50 – 90
Weight (lb)			
N	861	277	846
Mean ± SD	188.3 ± 48.6	185.6 ± 45.8	188.1 ± 46.4
Median	181.0	183.0	182.0
Range	88 - 425	96 - 368	88 – 401
<100	3 (0.3)	1 (0.4)	4 (0.5)
100 - <150	169 (19.6)	56 (20.2)	165 (19.5)
150 - <200	406 (47.2)	126 (45.5)	381 (45.0)
200 - <250	190 (22.1)	71 (25.6)	209 (24.7)
250 - <300	65 (7.5)	19 (6.9)	67 (7.9)
>=300	28 (3.3)	4 (1.4)	20 (2.4)
BMI (kg/m^2)			
N	861	277	845
Mean ± SD	30.3 ± 7.2	29.9 ± 6.7	30.4 ± 7.1
Median	28.7	29.1	29.5
Range	17 - 71	17 - 59	16 – 65

* Unless otherwise indicated, the number of subjects used to calculate the mean values is given at the top of the table as Total subjects.
SD = standard deviation; BMI = body mass index

(The table above is taken from Table 5-2 on Page 33 of Module 2.5 Clinical Overview provided by Novartis for Lansoprazole delayed-release capsules 15 mg)

Table 3. Demographic features by studies

Study No	PRSW-GN-301		PRSW-GN-302		PRSW-GN-305		
Demographic characteristic	Lansoprazole 15 mg (N = 282)	Placebo (N = 282)	Lansoprazole 15 mg (N = 288)	Placebo (N = 282)	Lansoprazole 15 mg (N = 291)	Placebo (N = 284)	Lansoprazole 30 mg (N = 277)
Age							
Mean ± SD	46.3 ± 13.8	48.1 ± 13.8	49.5 ± 14.1	47.6 ± 13.2	48.2 ± 14.5	47.4 ± 13.7	48.8 ± 14.1
Median (Min – Max)	46.0 (18 – 90)	48.0 (18 – 86)	50.0 (20 – 84)	48.0 (18 – 81)	49.0 (18 – 85)	48.0 (19 – 85)	49.0 (18 – 85)
Gender – n (%)							
Male	104 (36.9)	100 (35.5)	96 (34.0)	92 (32.6)	118 (40.5)	103 (36.3)	94 (33.9)
Female	178 (63.1)	182 (64.5)	190 (66.0)	190 (67.4)	173 (59.5)	181 (63.7)	183 (66.1)
Race – n (%)							
Caucasian	195 (69.1)	195 (69.1)	218 (75.7)	209 (74.1)	196 (67.4)	183 (64.4)	191 (69.0)
Black	26 (9.2)	30 (10.6)	32 (11.1)	32 (11.3)	39 (13.4)	38 (13.4)	41 (14.8)
Hispanic	39 (13.8)	39 (13.8)	34 (11.8)	39 (13.8)	44 (15.1)	45 (15.8)	35 (12.6)
Asian	11 (3.9)	9 (3.2)	1 (0.3)	1 (0.4)	10 (3.4)	12 (4.2)	9 (3.2)
Other	11 (3.9)	9 (3.2)	3 (1.0)	1 (0.4)	2 (0.7)	6 (2.1)	1 (0.4)
Weight (lb)							
Mean ± SD	186.7 ± 46.9	185.2 ± 47.9	188.5 ± 49.6	188.0 ± 44.2	189.7 ± 49.4	190.9 ± 46.9	185.6 ± 45.8
Median (Min – Max)	180.0 (104 – 370)	179.5 (92 – 401)	183.5 (95 – 425)	180.0 (88 – 319)	181.0 (88 – 398)	190.0 (96 – 360)	183.0 (96 – 368)
Height (in)							
Mean ± SD	66.3 ± 3.9	65.9 ± 4.1	65.8 ± 3.6	66.0 ± 4.1	66.2 ± 4.0	66.2 ± 3.8	66.1 ± 4.2
Median (Min – Max)	66.0 (52 – 76)	65.0 (51 – 77)	65.0 (57 – 75)	65.0 (56 – 90)	66.0 (57 – 76)	65.0 (50 – 77)	65.0 (54 – 78)
BMI (kg/m^2)							
Mean ± SD	30.0 ± 7.1	30.0 ± 7.0	30.5 ± 7.3	30.4 ± 6.9	30.5 ± 7.4	30.8 ± 7.5	29.9 ± 6.7
Median (Min – Max)	28.3 (18 – 56)	29.2 (16 – 65)	29.2 (17 – 69)	29.3 (16 – 55)	29.1 (18 – 71)	30.0 (17 – 60)	29.1 (17 – 59)

(The table above is taken from Table 4-2 on Page 18 of Summary of Clinical Efficacy provided by the Applicant.)

Overall, the subjects across the studies were primarily Caucasian (70.7% in the lansoprazole 15 mg group, 69.0% in the lansoprazole 30 mg group, and 69.2% in the placebo group). The percentages of Hispanic and Black subjects were similar in all three studies. The percentages of males to females were 37.2% to 62.8% (respectively) in the lansoprazole 15 mg group, 33.9% to 66.1% (respectively) in the lansoprazole 30 mg group, and 34.8% to 65.2% (respectively) in the placebo group. The BMI parameters were similar amongst the subjects in all three groups. The mean BMI was 30.3 for the lansoprazole 15 mg group, 29.9 for the lansoprazole 30 mg group, and 30.4 for the placebo group (see Table 2).

By study, there were no major differences in the patient populations enrolled with regard to baseline demographic characteristics. The majority of subjects enrolled in the 3 studies were female (please refer to Table 3).

Baseline Disease Characteristics

Pertinent baseline disease characteristics are summarized in the table below.

Table 4. Disease characteristics – Controlled studies (Intent to Treat set)

Study No	PRSW-GN-301				PRSW-GN-302				PRSW-GN-305			
Disease characteristic	Lansoprazole 15 mg (N = 282)		Placebo (N = 282)		Lansoprazole 15 mg (N = 288)		Placebo (N = 282)		Lansoprazole 15 mg (N = 291)		Placebo (N = 284)		Lansoprazole 30 mg (N = 277)	
No. of days with heartburn/ week in last month (mean ± SD)	4.1 ± 1.5		4.0 ± 1.6		4.0 ± 1.5		4.0 ± 1.5		3.9 ± 1.4		4.0 ± 1.4		4.0 ± 1.4	
Subject's rating of most intense episode of heartburn experienced in last month – n (%) [a]														
Mild	27	(9.6)	38	(13.5)	36	(12.5)	25	(8.9)	29	(10.0)	22	(7.7)	17	(6.1)
Moderate	202	(71.6)	202	(71.6)	203	(70.7)	216	(76.6)	196	(67.4)	208	(73.2)	197	(71.1)
Severe	53	(18.8)	42	(14.9)	48	(16.7)	41	(14.5)	66	(22.7)	54	(19.0)	63	(22.7)
Any prescription/ OTC treatment for heartburn over past 5 years – n (%)	269	(95.4)	267	(94.7)	266	(92.4)	266	(94.3)	279	(95.9)	267	(94.0)	260	(93.9)
Subject has had heartburn symptom initiator of – n (%)														
Food and/or beverage	277	(98.2)	270	(95.7)	275	(95.5)	271	(96.1)	281	(96.6)	273	(96.5)	263	(94.9)
Stress and/or anxiety	148	(52.5)	157	(55.7)	164	(56.9)	153	(54.3)	159	(54.6)	167	(59.0)	155	(56.0)
Lying down	160	(56.7)	162	(57.4)	165	(57.3)	160	(56.7)	215	(73.9)	208	(73.5)	202	(72.9)
Hectic lifestyle	103	(36.5)	101	(35.8)	90	(31.3)	101	(35.8)	82	(28.2)	80	(28.3)	93	(33.6)
Physical activity	46	(16.3)	56	(19.9)	48	(16.7)	66	(23.4)	53	(18.2)	40	(14.1)	50	(18.1)
Medication	40	(14.2)	41	(14.5)	25	(8.7)	26	(9.2)	34	(11.7)	27	(9.5)	38	(13.7)

[a] Mild: Heartburn is present but easily tolerated.
Moderate: Heartburn is sufficient to cause interference with normal daily activities or sleep.
Severe: Heartburn is incapacitating. Subject is unable to perform normal daily activities or sleep.

(Table above is obtained from Table 3-2 on Page 20 of the Applicant's Summary of Clinical Efficacy.)

In Studies 301 and 302, the disease characteristics were similar (Table 4). However, the proportion of subjects in Study 305 that rated their most recent episode as severe was slightly higher than in Studies 301 and 302. Also, the proportion of subjects that stated that lying down was an initiator of heartburn symptoms was higher in Study 305 than in Studies 301 and 302.

The subjects' distribution of daytime and nighttime heartburn during the Run-in period is summarized in the table below.

Table 5. Distribution of heartburn symptoms (day and night)

Study No	PRSW-GN-301	PRSW-GN-302	PRSW-GN-305
Time of day of heartburn occurrence	(N = 564)	(N = 570)	(N = 852)
Daytime only	27%	26%	0%
Nighttime only	2%	1%	4%
Some nighttime	73%	74%	100%
≥ 2 nighttimes	51%	52%	100%

(Table above is taken from Table 3-3 on Page 21 of the Applicant's Summary of Clinical Efficacy.)

Approximately 74% of the subjects enrolled in Studies 301 and 302 reported at least 1 episode of nighttime heartburn during the Run-in phase compared to 100% of subjects enrolled in Study 305.

6.1.3 Subject Disposition

The subject disposition for each of the three studies is summarized in the table below.

Table 6. Study participation and withdrawals – controlled studies (Intent to Treat set)

Study No	PRSW-GN-301				PRSW-GN-302				PRSW-GN-305					
Disposition	Lansoprazole 15 mg		Placebo		Lansoprazole 15 mg		Placebo		Lansoprazole 15 mg		Placebo		Lansoprazole 30 mg	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Planned	288		288		288		288		288		288		288	
Randomized/exposed	282	(100.0)	282	(100.0)	288	(100.0)	282	(100.0)	291	(100.0)	284	(100.0)	277	(100.0)
Completed to end of Treatment phase	272	(96.5)	274	(97.2)	278	(96.5)	270	(95.7)	281	(96.6)	273	(96.1)	265	(95.7)
Completed study	269	(95.4)	271	(96.1)	276	(95.8)	269	(95.4)	278	(95.5)	272	(95.8)	264	(95.3)
Discontinued:	13	(4.6)	11	(3.9)	12	(4.2)	13	(4.6)	13	(4.5)	12	(4.2)	13	(4.7)
Adverse event(s)	2	(0.7)	2	(0.7)	3	(1.0)	2	(0.7)	3	(1.0)	3	(1.1)	4	(1.4)
Protocol deviation	1	(0.4)	2	(0.7)	0	(0.0)	0	(0.0)	1	(0.3)	2	(0.7)	0	(0.0)
Withdrew consent	4	(1.4)	5	(1.8)	3	(1.0)	5	(1.8)	4	(1.4)	5	(1.8)	8	(2.9)
Lost to follow-up	5	(1.8)	2	(0.7)	3	(1.0)	5	(1.8)	4	(1.4)	1	(0.4)	1	(0.4)
Administrative problems	1	(0.4)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.3)	1	(0.4)	0	(0.0)
Lack of efficacy	0	(0.0)	0	(0.0)	2	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)

(The table above is taken from Table 3-5 on Page 24 of the Summary of Clinical Efficacy provided by the Applicant.)

There were 1986 subjects who were enrolled in the clinical trials for the treatment of frequent heartburn; 1138 subjects were treated with lansoprazole (861 received lansoprazole 15 mg and 277 received lansoprazole 30 mg) and 848 were treated with placebo. At least 95% of the subjects in each study and in each treatment group completed the study.

6.1.4 Analysis of Primary Endpoint(s)

Studies 301 and 302

Proportion of 24-hour days with no heartburn over 14 days of treatment

The primary efficacy endpoint in Studies 301 and 302 was the proportion of 24-hour days with no heartburn during 14 days of treatment (please refer to Table 7 below). The assessment of efficacy was based on the subject's daily self-assessment regarding the occurrence of heartburn episodes during the 14-day double-blind treatment period. The efficacy variables included the proportion of heartburn-free days and nighttimes as reported by the subjects. It was analyzed as the percentage of 24-hour days between Day 1 and Day 14, inclusively, with no heartburn (daytime or nighttime). The mean percentage of 24-hour days between Day 1 and Day 14, inclusively, with no heartburn, 95% confidence limits on the mean, and median, minimum and maximum values were calculated for each treatment. The 2 treatment groups were compared by fitting an analysis of covariance (ANCOVA) to the percentage of 24-hour days with no heartburn, including treatment and center as factors and the proportion of 24-hour days on which heartburn was experienced during the Run-in phase as a covariate.

Table 7. Proportion (%) of 24-hour days with no heartburn over 14 days of treatment (301 and 302; ITT)

Study No / Statistic	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg	p-value +
Study PRSW-GN-301				
n	282	282	-	
Mean (95% C.I.)	59.9 (56.4, 63.4)	45.7 (42.4, 49.0)		< 0.0001
Median	64.3	50.0		
Min – Max	0.0 – 100.0	0.0 – 100.0		
Study PRSW-GN-302				
n	288	282	-	
Mean (95% C.I.)	64.7 (61.1, 68.2)	45.0 (41.6, 48.4)		< 0.0001
Median	71.4	50.0		
Min – Max	0.0 – 100.0	0.0 – 100.0		

+ p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

(Table above is modified from Table 3-15 on Page 41 of the Applicant's Summary of Clinical Efficacy)

In Study 301, the proportion of 24-hour days with no heartburn over 14 days of treatment was 59.9% in the subjects receiving 15 mg of lansoprazole and 45.7% in the placebo group ($p < 0.0001$).

Study 302 revealed a 64.7% mean value in the group receiving lansoprazole 15 mg vs. a 45.0% mean value in the placebo group ($p < 0.0001$).

Medical Officer Comments:

The primary endpoint definition for Studies 301 and 302 and the methods for the primary efficacy analysis are acceptable. For each of the studies, there was a statistically significant difference in the response rates between the treatment and placebo arm; the p-value for each of the studies was less than 0.0001. Thus, the data does support the Applicant's claim that OTC lansoprazole at 15 mg is efficacious in the treatment of heartburn in a 24 hour day over the course of 14 days.

Study 305

Proportion of nighttimes with no heartburn over 14 days of treatment

The primary efficacy endpoint in Study 305 was the proportion of nighttimes with no heartburn during 14 days of treatment with 15 mg of lansoprazole per day.

Table 8. Proportion (%) of nighttimes with no heartburn over 14 days of treatment – 305 (ITT)

Study No / Statistic	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg	p-value +
Study PRSW-GN-305				
n	291	284	277	(1) <0.0001
Mean (95% C.I.)	61.7 (57.7, 65.6)	47.8 (44.1, 51.5)	61.3 (57.2, 65.4)	(2) <0.0001
Median	71.4	50.0	71.4	(3) 0.6610
Min – Max	0.0 – 100.0	0.0 – 100.0	0.0 – 100.0	

+ p-value is based on a nonparametric ANCOVA with treatment and center as factors and the proportion of nighttimes with heartburn during the Run-in phase as a covariate.

(1) p-value for comparison of lansoprazole 15 mg and placebo.
(2) p-value for comparison of lansoprazole 30 mg and placebo.
(3) p-value for comparison of lansoprazole 15 mg and lansoprazole 30 mg.

(Table above is modified from Table 3-20 on Page 46 of Module 2.7.3 Summary of Clinical Efficacy provided by Novartis for Lansoprazole delayed-release capsules 15 mg)

The primary efficacy variable in Study 305 was the proportion of nighttimes with no heartburn during 14 days of treatment (please refer to Table 8). The evaluation of nighttime heartburn began upon going to bed and ended with the next dose of study medication which was to be taken immediately after the subject had awoken. The variable was analyzed as the percentage of nighttimes between Day 1 and Day 14, inclusive, with no heartburn. Missing values were handled in a similar manner to missing values for the proportion of 24-hour days with no heartburn, substituting nighttimes for 24-hour days. The proportion of nighttimes with no heartburn over the 14 day period revealed a mean value of 61.7% in the group whose subjects received 15 mg of lansoprazole and a value of 47.8% in the placebo group ($p < 0.0001$). The proportion of nighttimes with no heartburn over the 14 day period revealed a mean value of 61.3% in the group whose subjects received 30 mg of lansoprazole and a value of 47.8% in the placebo group ($p < 0.0001$).

Medical Officer Comments:

The primary endpoint definition for Study 305 and the methods for the primary efficacy analysis are acceptable.

There was a statistically significant difference in the response rates between the treatment arm and placebo arm; the p-value was less than 0.0001. However, by reviewing these results, one cannot conclude that OTC lansoprazole is efficacious for the treatment of nighttime heartburn over a 14 day treatment period. The reasons for this are that the definition of nighttime heartburn has not been established and there are several different, unrelated etiologies that contribute to nighttime heartburn. These factors are discussed at length in Section 9.2 under the heading, "Labeling Recommendations." Additionally, it is unclear as to when the subjects were taking the 15 mg of lansoprazole. If a subject had taken the lansoprazole (15 mg) before dinner instead of the usual recommendation of taking it before breakfast, then in reality, the subject's "day" would have started at nighttime and it would be incorrect to conclude that the relief of heartburn at nighttime (in the eyes of the investigators) was due to the lansoprazole; by taking the lansoprazole prior to dinner, the subject, in effect, had reversed the daytime and nighttime occurrences. An investigator would be misinterpreting the subject's relief of nighttime heartburn since the subject, unbeknownst to the investigator, had taken the 15 mg of lansoprazole before dinner instead of before breakfast. This would have caused a reversal of the night and day data without the knowledge of the investigator.

It should also be noted that lansoprazole 30 mg did not appear to have a higher response rate compared to placebo than lansoprazole 15 mg for the primary endpoint.

6.1.5 Analysis of Secondary Endpoints

Studies 301 and 302

Proportion of Nighttimes with no Heartburn Over 14 Days

A secondary efficacy endpoint in Studies 301 and 302 was the proportion of nighttimes with no heart-burn over 14 days of treatment (please refer to Table 9).

Table 9. Proportion (%) of nighttimes with no heartburn over 14 days of treatment (301 & 302; ITT)

Study No / Statistic	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg	p-value +
Study PRSW-GN-301				
n	282	282	-	
Mean (95% C.I.)	79.5 (76.5, 82.5)	76.3 (73.3, 79.4)		0.0029
Median	90.3	85.7		
Min – Max	0.0 – 100.0	0.0 – 100.0		
Study PRSW-GN-302				
n	288	282	-	
Mean (95% C.I.)	81.6 (78.8, 84.5)	77.0 (74.0, 80.0)		<0.0001
Median	91.7	85.7		
Min – Max	0.0 – 100.0	0.0 – 100.0		

+ p-value is based on a nonparametric ANCOVA with treatment and center as factors and the proportion of nighttimes with heartburn during the Run-in phase as a covariate.

(Table above is modified from Table 3-16 on Page 42 of Module 2.7.3 Summary of Clinical Efficacy provided by Novartis for Lansoprazole delayed-release capsules 15 mg)

In Study 301, the proportion of nighttimes with no heartburn over 14 days of treatment was 79.5% in the subjects receiving 15 mg of lansoprazole and 76.3% in the placebo group (p=0.0029).

Study 302 revealed an 81.6% mean value in the group receiving lansoprazole 15 mg vs. a 77.0% mean value in the placebo group (p<0.0001).

Proportion of 24-hour days with no heartburn over Days 1 through 2

Another secondary efficacy endpoint in Studies 301 and 302 was the proportion of 24-hour days with no heartburn over Days 1 through 2 (please refer to Table 10). This was analyzed as the percentage of subjects with each total number and proportion of heartburn-free 24-hour days during Days 1 through 2.

Table 10. Proportion of 24-hour days with no heartburn over Days 1 through 2 of the 14 day treatment period – controlled studies (Intent to Treat set)

Number (proportion) of 24-hour days with no heartburn	Lansoprazole 15 mg		Placebo		Lansoprazole 30 mg		p-value +
	n	(%)	n	(%)	n	(%)	
Study PRSW-GN-301	(N = 282)		(N = 282)				
0 (0%)	85	(30.1)	122	(43.3)	-		
1 (50%)	105	(37.2)	97	(34.4)	-		0.0006
2 (100%)	92	(32.6)	63	(22.3)	-		
Study PRSW-GN-302	(N = 288)		(N = 282)				
0 (0%)	86	(29.9)	124	(44.0)	-		
1 (50%)	91	(31.6)	90	(31.9)	-		<0.0001
2 (100%)	111	(38.5)	68	(24.1)	-		

+ p-value is based on a CMH test stratified by center.

(Table above is modified from Table 3-17 on Page 43 of Module 2.7.3 Summary of Clinical Efficacy provided by Novartis for Lansoprazole delayed-release capsules 15 mg)

The differences between lansoprazole 15 mg and placebo in the proportions of subjects who were heartburn-free on at least 1 of the first 2 days in the 14 day Treatment phase are noted as 2.8% and -0.3%, respectively, for Studies 301 and 302 (Table 10). The differences between lansoprazole 15 mg and placebo in the proportions of subjects who were completely heartburn-free over Days 1-2 were as follows: 10.3% and 14.4%, respectively, for Studies 301 and 302 (Table 10).

Proportion of Subjects with no Heartburn on Day 1

Another secondary efficacy endpoint for Studies 301 and 302 was the proportion of subjects with no heartburn on Day 1 (please refer to Table 11). The number and percentage of subjects who had no heartburn (daytime or nighttime) on Day 1 were calculated for each treatment group together with the 95% confidence interval on each proportion. The difference in success rates between the 2 treatment groups was calculated, with its 95% confidence interval. Efficacy was analyzed using the CMH test stratified by center. A logistic regression model adjusting for center and the proportion of 24-hour days with heartburn during the Run in phase was also fitted, and the odds ratio for the treatment effect was calculated, with its 95% confidence interval. The proportion differences between the subjects in each group receiving lansoprazole vs. the subjects in the placebo group are as follows:

Table 11. Proportion of subjects with no heartburn for 24 hours on Day 1 of treatment – controlled studies (Intent to Treat set)

Treatment	N	Proportion of subjects with no heartburn for 24 hours on Day 1			p-value +
		n/N	(%)	(95% C.I.)	
Study PRSW-GN-301					
Lansoprazole 15 mg	282	142/282	50.4	(44.5, 56.2)	
Placebo	282	93/282	33.0	(27.5, 38.5)	
Difference between treatments:					
Lansoprazole 15 mg – Placebo			17.4	(9.2, 25.5)	< 0.0001
Study PRSW-GN-302					
Lansoprazole 15 mg	288	146/288	50.7	(44.9, 56.5)	
Placebo	282	107/282	37.9	(32.3, 43.6)	
Difference between treatments:					
Lansoprazole 15 mg – Placebo			12.8	(4.6, 20.9)	0.0011

+ p-value is based on a CMH test stratified by center.

(Table above is modified from Table 3-18 on Page 44 of Module 2.7.3 Summary of Clinical Efficacy provided by Novartis for Lansoprazole delayed-release capsules 15 mg)

In Study 301, there was a 17.4% difference between the subjects with no heartburn for 24 hours on Day 1 in the group receiving 15 mg of lansoprazole and the placebo group ($p < 0.0001$). In Study 302, there was a 12.8% difference between the subjects with no heartburn for 24 hours on Day 1 in the group receiving 15 mg of lansoprazole and the placebo group ($p = 0.0011$).

Medical Officer Comments:

The secondary endpoint definitions for Studies 301 and 302 and the methods for the secondary efficacy analyses are acceptable.

A higher proportion of nighttimes with no heartburn over the 14 day period was seen in the lansoprazole 15 mg group than in the placebo group for each of the studies (301 and 302).

The results for the endpoint of proportion of 24-hour days with no heartburn over Days 1 through 2 were also similar for Studies 301 and 302; each of the studies revealed a higher proportion in the lansoprazole group than the placebo group that were heartburn-free for two 24-hour days.

The results for the endpoint of proportion of subjects with no heartburn on Day 1 were also similar for Studies 301 and 302; each of the studies showed that there was a higher proportion in the lansoprazole group than the placebo group with complete relief of heartburn on Day 1. These results support the Applicant's claim that lansoprazole 15 mg can be efficacious in complete relief of heartburn in some patients even on Day 1 of a 14 day trial period.

Study 305

Proportion of 24-hour days with no heartburn over 14 Days

A secondary efficacy endpoint in Study 305 was the proportion of 24 hour days with no heartburn over Days 1 through 2 (please refer to Table 12).

Table 12. Proportion of 24-hour days with no heartburn over 14 days of treatment (305; ITT)

Study No / Statistic	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg	p-value +
Study PRSW-GN-305				
n	291	284	277	(1) < 0.0001
Mean (95% C.I.)	49.7 (45.8, 53.6)	29.5 (26.2, 32.8)	50.9 (46.7, 55.1)	(2) < 0.0001
Median	57.1	24.1	57.1	(3) 0.7686
Min – Max	0.0 – 100.0	0.0 – 100.0	0.0 – 100.0	

+ p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

(1) p-value for comparison of lansoprazole 15 mg and placebo.
(2) p-value for comparison of lansoprazole 30 mg and placebo.
(3) p-value for comparison of lansoprazole 15 mg and lansoprazole 30 mg.

(Table above is modified from Table 3-19 on Page 47 of the Applicant's Summary of Clinical Efficacy.)

This study revealed that during the 14 day period, subjects receiving 15 mg of lansoprazole experienced 49.7% 24-hour days with no heartburn as compared to the subjects in the placebo group who experienced 29.5% 24-hour days with no heartburn ($p < 0.0001$). Subjects receiving 30 mg of lansoprazole experienced 50.9% 24-hour days with no heartburn as compared to the subjects in the placebo group who experienced 29.5% 24-hour days with no heartburn ($p < 0.0001$).

Proportion of Subjects with No Heartburn on Day 1

Another secondary endpoint in Study 305 was the proportion of subjects with no heartburn on Day 1 (please refer to Table 13).

Table 13. Proportion of subjects with no heartburn for 24 hours on Day 1 of treatment – (Intent to Treat set)

Treatment	N	Proportion of subjects with no heartburn for 24 hours on Day 1			p-value +
		n/N	(%)	(95% C.I.)	
Study PRSW-GN-305					
Lansoprazole 15 mg	291	103/291	35.4	(29.9, 40.9)	
Placebo	284	64/284	22.5	(17.7, 27.4)	
Lansoprazole 30 mg	277	101/277	36.5	(30.8, 42.1)	
Difference between treatments:					
Lansoprazole 15 mg – Placebo			12.9	(5.4, 20.3)	0.0005
Lansoprazole 30 mg – Placebo			13.9	(6.4, 21.5)	0.0004
Lansoprazole 15 mg – Lansoprazole 30 mg			-1.1	(-9.0, 6.8)	0.9764

+ p-value is based on a CMH test stratified by center.

(Table above is modified from Table 3-22 on Page 48 of the Applicant's Summary of Clinical Efficacy.)

There was a 12.9% difference between the subjects with no heartburn for 24 hours on Day 1 in the group receiving 15 mg of lansoprazole and the placebo group (p=0.0005). There was a 13.9% difference between the subjects with no heartburn for 24 hours on Day 1 in the group receiving 30 mg of lansoprazole and the placebo group (p=0.0004).

Medical Officer Comments:

The results for each of the secondary efficacy endpoints in Study 305 were similar to those for the corresponding efficacy endpoint in Studies 301 and 302.

There was a higher proportion of 24-hour days with no heartburn over 14 days in the lansoprazole 15 mg group than in the placebo group. This reviewer agrees with the Applicant's premise that relief of heartburn is noted over the course of a 24-hour day during a 14 day period through the use of lansoprazole 15 mg.

Also, there was a higher proportion of subjects in the lansoprazole 15 mg group than in the placebo group with complete relief of heartburn on Day 1. These results support the Applicant's claim that lansoprazole 15 mg can be efficacious in complete relief of heartburn in some patients even on Day 1 of a 14 day trial period.

It should also be noted that lansoprazole 30 mg did not appear to have a higher response rate compared to placebo than lansoprazole 15 mg for either of these secondary endpoints.

6.1.6 Other Endpoints

Proportion of 24-hour Days with No Heartburn over Days 1 through 2

The tertiary efficacy endpoint in Study 305 was the proportion of 24-hour days with no heartburn over Days 1 through 2 (please refer to Table 14 below).

Table 14. Proportion of 24-hour days with no heartburn over Days 1-2 of the 14 day treatment period

Number (proportion) of 24-hour days with no heartburn	Lansoprazole 15 mg		Placebo		Lansoprazole 30 mg		p-value +
	n	(%)	n	(%)	n	(%)	
Study PRSW-GN-305	(N = 291)		(N = 284)		(N = 277)		
0 (0%)	138	(47.4)	182	(64.1)	125	(45.1)	(1) < 0.0001
1 (50%)	94	(32.3)	70	(24.6)	78	(28.2)	(2) < 0.0001
2 (100%)	59	(20.3)	32	(11.3)	74	(26.7)	(3) 0.2857

+ p-value is based on a CMH test stratified by center.

(1) p-value for comparison of lansoprazole 15 mg and placebo.
(2) p-value for comparison of lansoprazole 30 mg and placebo.
(3) p-value for comparison of lansoprazole 15 mg and lansoprazole 30 mg.

(Table above is modified from Table 3-17 on Page 43 of the Applicant's Summary of Clinical Efficacy.)

The difference between lansoprazole 15 mg and placebo in the proportion of subjects who were heartburn-free on at least 1 of the first 2 days in the 14 day Treatment phase was 7.7%. The difference between lansoprazole 15 mg and placebo in the proportion of subjects who were completely heartburn-free over Days 1-2 was 9.0% ($p < 0.0001$).

The difference between lansoprazole 30 mg and placebo in the proportion of subjects who were heartburn-free on at least 1 of the first 2 days in the 14 day Treatment phase was 3.6%. The difference between lansoprazole 30 mg and placebo in the proportion of subjects who were completely heartburn-free over Days 1-2 was 15.4% ($p < 0.0001$).

<u>Medical Officer Comments:</u>
The results for the tertiary efficacy endpoint in Study 305 are similar to that of the corresponding efficacy endpoint in Studies 301 and 302. There was a higher proportion of subjects in the lansoprazole 15 mg group than in the placebo group who were completely heartburn-free over Days 1 through 2. This reviewer is in agreement with the Applicant that some patients can achieve complete heartburn relief over Days 1 through 2 through the use of 15 mg of lansoprazole over a 14 day course.

It should also be noted that lansoprazole 30 mg did not appear to have a higher response rate compared to placebo than lansoprazole 15 mg for this tertiary endpoint.

6.1.7 Subpopulations

Demographic Characteristics:
Across demographic categories, the treatment effect was comparable for the primary efficacy variable, proportion of 24-hour days with no heartburn. The proportions of 24-hour days with no heartburn over 14 days of treatment by age, gender, and race are provided in Table 17 in Appendix 10.1.

Nighttime Heartburn Symptoms:
The population enrolled in Study 305 differed from that enrolled in Studies 301 and 302; a key enrollment criterion in Study 305 was that subjects have frequent nighttime heartburn ($\geq$ 2 mean nighttime heartburn episodes per week). Approximately 74% of the subjects enrolled in Studies 301 and 302 reported at least 1 episode of nighttime heartburn during the Run-in phase compared to 100% of subjects enrolled in Study 305 (please refer to Table 5 in Section 6.1.2).

The proportion of 24-hour days with no heartburn over the 14 days of lansoprazole 15 mg treatment in Studies 301 and 302 (mean 59.9% and 64.7%; see Table 7) appeared to be higher than the corresponding proportion in Study 305 (mean 49.7%; see Table 12). However, the treatment effect was generally similar across the three studies.

The proportion of nighttimes with no heartburn over the 14 days of lansoprazole 15 mg treatment in Studies 301 and 302 (mean 79.5% and 81.6%; see Table 9) appeared to be higher than the corresponding proportion in Study 305 (mean 61.7%; see Table 8). However, the treatment effect in Study 305 appeared to be greater than that in Studies 301 and 302.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosage (15 mg) recommended by the Applicant for OTC lansoprazole for the treatment of heartburn for a 14-day period is consistent with the lowest dosage of lansoprazole that was initially approved and is currently available through prescription in the United States.

Medical Officer Comments:
The Applicant's approach with regards to the dosing for OTC lansoprazole is reasonable. The data supplied by the Applicant in the three trials does support the Applicant's claim of relief of frequent heartburn occurring two or more days a week for 14 days by lansoprazole delayed release capsule 15 mg for over the counter (OTC) marketing. The data showed efficacy and the margin of safety is acceptable [please refer to the review by Dr. Lolita Lopez, medical officer at The Division of Nonprescription Clinical Evaluation (DNCE) under the same NDA].

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The history of PPI's for the treatment of heartburn has been documented and the extensive data has been closely evaluated at length in the past. This class of medications has shown solid

efficacy for the treatment of heartburn. Specifically, lansoprazole 15 mg has been prescribed by physicians in the United States since 1995 and no efficacy issues or tolerance effects have been noted. Given that the Applicant is adhering to the lower prescription dose for OTC lansoprazole and no significant changes from the original prescription structure have been proposed, no new recommendations are made by this reviewer at this time.

However, several points of note should be considered regarding the treatment of frequent heartburn over a two week period. First, a period of 14 continuous days is needed for the treatment course, and one to 4 days are needed for the full effects of OTC lansoprazole to become apparent. The efficacy results have been consistent with this statement; although some efficacy was noted in the treatment of frequent heartburn over the first 24 hours (Table 11), a full 4 days are needed for the full efficacy of the medication to become apparent (see Tables 9 and 10). Second, it is of paramount importance to note that the OTC treatment of frequent heartburn by lansoprazole consists of a 14 day period as proposed by the Applicant, and that any need for additional days beyond the 14 day course will need further evaluation by a physician and the workup that it would ensue.

6.1.10 Additional Efficacy Issues/Analyses

Major Labeling Recommendations

Major issues with regard to the labeling related to efficacy are described below. A full listing of labeling recommendations is provided in Section 9.2.

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Efficacy Results Combined Across Studies

Proportion of 24-hour days with no heartburn over 14 days of treatment

The combined efficacy results across all three studies are shown below (Table 15).

Table 15. Proportion (%) of 24-hour days with no heartburn over 14 days of treatment – combined efficacy data (Intent to Treat set)

Statistic	Lansoprazole 15 mg (N = 861)	Placebo (N = 848)	p-value +
n	861	848	
Mean (95% C.I.)	58.0 (55.9, 60.2)	40.0 (38.0, 42.0)	< 0.0001
Median	64.3	42.9	
Min – Max	0.0 – 100.0	0.0 – 100.0	

+ p-value is based on an ANCOVA with treatment and center as factors and the proportion of days with heartburn during the Run-in phase as a covariate.

(Table above is obtained from Table 3-24 on Page 53 of Module 2.7.3 Summary of Clinical Efficacy provided by Novartis for Lansoprazole delayed-release capsules 15 mg)

Based on the combined results, the following mean values for the proportion of 24-hour days with no heartburn over the 14 days of treatment were found: 58.0% for the group receiving 15 mg of lansoprazole and 40.0% in the placebo group ($p < 0.0001$).

Proportion of Nighttimes with No Heartburn over 14 Days of Treatment

The combined efficacy results across all three studies are shown below (Table 16).

Table 16. Proportion (%) of nighttimes with no heartburn over 14 days of treatment – combined efficacy data (ITT)

Statistic	Lansoprazole 15 mg (N = 861)	Placebo (N = 848)	p-value +
n	861	848	
Mean (95% C.I.)	74.2 (72.2, 76.2)	67.0 (64.9, 69.1)	< 0.0001
Median	85.7	78.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	

+ p-value is based on a nonparametric ANCOVA with treatment and center as factors and the proportion of days with heartburn during the Run-in phase as a covariate.

(Table above is obtained from Table 3-25 on Page 55 of Module 2.7.3 Summary of Clinical Efficacy provided by the Applicant.)

Based on the combined efficacy results, the following mean values for the proportion of 24-hour days with no heartburn over the 14 days of treatment were found: 74.2% for the group receiving 15 mg of lansoprazole and 67.0% in the placebo group ($p< 0.0001$).

7 Review of Safety

For a full review of safety, please refer to the review performed by Dr. Lolita Lopez in the Division of Nonprescription Clinical Evaluation (DNCE) under the same NDA (NDA 22-327).

8 Postmarket Experience

For a full review of safety, please refer to the review performed by Dr. Lolita Lopez in the Division of Nonprescription Clinical Evaluation (DNCE) under the same NDA (NDA 22-327).

9 Appendices

9.1 Literature Review/References

Please refer to the citations that have already been provided in the footnotes and to the references that have been noted in the review.

9.2 Labeling Recommendations

This reviewer is making several recommendations below regarding the proposed OTC label for lansoprazole.

Principle Display Panel (PDP)

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 1

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9.3 Advisory Committee Meeting

There was no Advisory Committee meeting required for this NDA because there is considerable experience with Prevacid (lansoprazole), and because there are no concerns related to safety or efficacy of Prevacid (lansoprazole) that would require recommendations from an Advisory Committee.

10 APPENDICES

10.1 Proportions of 24-hour Days with No Heartburn over 14 Days by Demographic Characteristics

Table 17. Proportion (%) of 24-hour Days with no Heartburn over 14 days of Treatment by Age – Combined Efficacy Data (Intent to Treat set)

Variable / Age	Lansoprazole 15 mg			Placebo			
	Mean (95% CI)	Median	N	Mean (95% CI)	Median	N	p-value
Percent 24-hour days with no heartburn							
< 65 years	58.1 (55.8, 60.4)	64.3	756	40.6 (38.5, 42.7)	42.9	744	<0.0001 +
≥ 65 years	57.7 (51.0, 64.5)	64.3	105	35.4 (29.7, 41.2)	35.7	104	<0.0001 +

+ p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

(Table above is modified from Table 3-27 on Page 58 of the Applicant's Summary of Clinical Efficacy.)

Table 18. Proportion (%) of 24-hour Days with no Heartburn over 14 days of Treatment by Gender – Combined Efficacy Data (Intent to Treat set)

Variable / Gender	Lansoprazole 15 mg			Placebo			
	Mean (95% CI)	Median	N	Mean (95% CI)	Median	N	p-value
Percent 24-hour days with no heartburn							
Male	60.6 (57.1, 64.0)	64.3	320	37.8 (34.2, 41.3)	35.7	295	<0.0001 +
Female	56.5 (53.8, 59.3)	64.3	541	41.2 (38.8, 43.6)	42.9	553	<0.0001 +

+ p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

(Table above is modified from Table 3-28 on Page 60 of the Applicant's Summary of Clinical Efficacy.)

Table 19. Proportion (%) of 24-hour Days with no Heartburn over 14 days of Treatment by Race – Combined Efficacy Data (Intent to Treat set)

Variable / Race	Lansoprazole 15 mg			Placebo			
	Mean (95% CI)	Median	N	Mean (95% CI)	Median	N	p-value
Percent 24-hour days with no heartburn							
Caucasian	62.6 (60.2, 65.0)	69.2	609	40.9 (38.6, 43.2)	42.9	587	<0.0001 +
Hispanic	43.2 (36.8, 49.6)	42.9	117	31.9 (26.8, 37.1)	28.6	123	0.0312 +
Other	50.4 (44.8, 55.9)	57.1	135	43.3 (38.0, 48.6)	42.9	138	0.0999 +

+ p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

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✓ Draft Labeling (b4)

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_____ Deliberative Process (b5)

Withheld Track Number: Medical- 2

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/s/

Ali Niak
4/14/2009 11:33:11 AM
MEDICAL OFFICER

Anil K Rajpal
4/14/2009 11:38:36 AM
MEDICAL OFFICER
I concur with Dr. Niak that the clinical effficacy review supports approval of lansoprazole 15 mg capsules for over-the-counter use, pending agreement on labeling.

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-327
Submission Code	000
Letter Date	July 15, 2008
Stamp Date	July 16, 2008
PDUFA Goal Date	May 16, 2009
Reviewer Name	Lolita A. Lopez, M.D.
Team Leader	Lesley-Anne Furlong, M.D.
Review Completion Date	March 11, 2009
Established Name	Lansoprazole
(Proposed) Trade Name	Prevacid 24-Hr
Therapeutic Class	Proton-Pump Inhibitor
Applicant	Novartis Consumer Health, Inc.
Priority Designation	S
Formulation	Delayed-Release Capsules
Dosing Regimen	15 mg Once Daily for 14 Days
Indication	Treatment of Frequent Heartburn
Intended Population	Adults (18 years and older)

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The proposed lansoprazole delayed release capsule 15 mg indicated for the relief of frequent heartburn occurring two or more days a week for 14 days has an acceptable safety profile for OTC marketing. Therefore, from a clinical safety standpoint, this reviewer recommends approval of the application. Final approvability depends on the clinical efficacy evaluation and the DSI inspection. In addition, the sponsor should incorporate the reviewing team's labeling recommendations for this product.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special risk management activities are recommended for this NDA.

1.2.2 Required Phase 4 Commitments

No required phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Lansoprazole (Prevacid®) is a proton-pump inhibitor (PPI) initially approved as a prescription product on May 10, 1995 for the treatment of acid-related gastrointestinal disorders. The prescription product is available in different formulations and dosage strengths. The sponsor, Novartis Consumer Health, Inc. (NCH), is seeking approval to market lansoprazole 15 mg delayed release capsules for over-the-counter (OTC) use in adults 18 years and older for the treatment of frequent heartburn (occurring two or more days a week). There are other products in the same class of drugs (omeprazole products) that are marketed OTC for the same indication.

In support of this NDA, the sponsor conducted three Phase III studies (PRSW-GN-301, PRSW-GN-302 and PRSW-GN-305) involving 1,986 patients. These trials studied comparable

subject populations and had similar study design. All studies were multicenter, double-blind, randomized, parallel group, placebo-controlled studies to investigate the safety and efficacy of lansoprazole 15 mg once daily in patients with frequent heartburn. Studies PRSW-GN-301 and -302 had identical study design and evaluated lansoprazole 15 mg once daily for 14 days for the treatment of frequent heartburn. Study 301 and Study 302 had the same efficacy endpoint: the proportion of 24-hr days with no heartburn over 14 days. Study PRSW-GN-305 investigated lansoprazole 30 mg in addition to lansoprazole 15 mg. The primary endpoint for Study 305 was the proportion of nighttimes with no heartburn over 14 days. Additional sources of safety data from postmarketing databases and literature search were also provided to support the safety of lansoprazole 15 mg.

This NDA is submitted under a 505(b)(1) application and relies on the Agency's previous finding of safety and efficacy for lansoprazole. NCH has an agreement with Takeda Abbott Pharmaceuticals (TAP), the holder of NDA 20-406 and IND 30,159 (Prevacid® delayed release capsules), granting NCH full right of reference to their data contained in these submissions in support of all NCH's applications related to the OTC use of Prevacid®.

1.3.2 Efficacy

Efficacy evaluation was based on the clinical studies conducted by NCH (PRSW-GN-301, PRSW-GN-302 and PRSW-GN-305) involving patients with frequent heartburn (occurring 2 or more days a week). The objective of the program was to demonstrate that a daily morning dose of lansoprazole 15 mg for 14 days was effective in increasing the proportion of days with no heartburn in frequent heartburn sufferers.

Efficacy of this NDA will be reviewed by the Division of Gastroenterology Products (DGP), see review entered in DFS.

1.3.3 Safety

Safety evaluation was based on data from the three clinical trials conducted by NCH, and from postmarketing safety databases including review of the medical literature. The clinical data utilized in the safety review to support the OTC use of lansoprazole 15 mg include:

- Safety data from clinical trials conducted by NCH (PRSW-GN-301, -302 and -305)
- Analysis of Global Postmarketing adverse events (AEs) received by TAP (May 1995 to September 2007)
- Analysis of FDA's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) (1969 to June 2007)
- Analysis of reports to the American Association of Poison Control Centers' (AAPCC) Toxic Exposure Surveillance System (TESS) database (2000-2006)
- Drug Abuse Warning Network (DAWN) report for lansoprazole (January 2003 to April 2007)
- World Health Organization's (WHO) summary of AE reports (October 1993 to July 2008)
- A review of medical literature relevant to the safety of lansoprazole (1988 to 2007)

- Current lansoprazole prescription label (U.S.)
- Safety Update

This safety review was focused on the single-ingredient lansoprazole 15 mg in adults, the proposed treatment regimen for OTC use. A total of 1,986 subjects participated in the three clinical efficacy trials; 1,138 were exposed to and received at least one dose of lansoprazole (861 received lansoprazole 15 mg, 277 received lansoprazole 30 mg) and 848 were treated with placebo. Each study comprised a 2-week placebo-controlled treatment phase, and a 1-week placebo follow-up phase. During the treatment phase, the gastrointestinal system had the most frequently reported AEs for each treatment group, and diarrhea was the most frequently observed AE occurring in 0.5% or more of subjects. Diarrhea was also the only AE suspected to be related to the study drug: lansoprazole 15 mg, 0.6% (5/861); lansoprazole 30 mg, 0.7% (2/277) compared to placebo, 0.1% (1/848). During the follow-up phase, the most frequently reported AEs were diarrhea in the 15 mg and 30 mg treatment groups compared to placebo (0.9% and 0.4% vs. 0%) and upper respiratory infection (0.7% and 0.4% vs. 0%). There were two reports of death, 1 each from the lansoprazole 15 mg and placebo group; neither was thought to be related to the administration of study medication. (See section 7.1.1)

In clinical trials conducted for prescription use, over 10,000 patients have been treated worldwide with lansoprazole in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. The following AEs were reported to have a possible or probable relationship to the drug in $\geq$ 1% lansoprazole treated patients and occurred at a greater rate in these patients than placebo-treated patients: diarrhea (3.8% vs. 2.3%), abdominal pain (2.1% vs. 1.2%), nausea (1.3% vs. 1.2%), and constipation (1% vs. 0.4%). The most commonly reported possibly or probably treatment-related AE during maintenance therapy was also diarrhea.[1]

Lansoprazole (Prevacid®) was first approved in the United States in May 1995. As of December 2007, the global patient exposure was estimated to be over ——— which includes all formulations worldwide with estimated U.S. sales of ——— prescriptions through June 2007. TESS reported 14,681 human exposures for lansoprazole with approximately 5,000 associated clinical effect (CE) terms from the years 2000 to 2006. Of these exposures, 60% (8,845) reported lansoprazole as the only substance ingested. Overall, the most frequently reported CEs were: drowsiness/lethargy 7.13%, tachycardia 3%, vomiting 2.5% and nausea 1.7%. Exposures resulted only in minor or moderate clinical effects when the only substance ingested was lansoprazole. In the FDA SRS/AERS database, a total of 4,704 cases were reported with 17,715 associated AE terms involving lansoprazole as a suspect medication from 1969 to 2007. Overall, the most common AEs reported were diarrhea 2.5%, condition aggravated 1.7%, nausea 1.5%, abdominal pain 1.3%, pyrexia 1.3%, drug interaction 1.2%, and headache 1%. In the WHO database, there were 6,609 cases involving 13,571 AE terms reported for lansoprazole. Two-thirds of these cases (70%; 4,606) involving 8,165 (60%) AE terms were reported from outside the United States., and the most frequently reported AE terms were diarrhea (6.5%), headache (4.5%), rash (3.7%), pruritus (3.4%), arthralgia (2.7%), nausea (2.5%), urticaria

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1 Prevacid Prescription Label, Adverse Reactions section (http://www.pdr.net) accessed 11-24-08.

(2.4%), dizziness (2.3%), and abdominal pain (2.1%). The DAWN data did not reveal any signal that lansoprazole is being abused or misused.

There was no conclusive evidence of a causal relationship between the use of lansoprazole and any previously unidentified serious or life-threatening adverse events from postmarketing experience. In the postmarketing database received by TAP, there were a total of 9,776 cases involving 17,768 AE terms from May 1995 to September 2007. Most cases (84%; 8,212) were non-serious, 13.8% (1,349) were serious[2], and 2.2% (215) were reports of death. Overall, the most commonly reported AE terms reported as having a rate of > 1% were: diarrhea (8.4%), nausea (3.9%), drug ineffective (3.8%), abdominal pain (3.2%), headache (2.7%), dizziness (2.1%), condition aggravated (2.1%), abdominal pain upper (1.7%) vomiting (1.6%), constipation (1.5%), flatulence (1.5%), rash (1.4%), alopecia (1.1%), and urticaria (1.1%).

The types of AEs reported during postmarketing and from the medical literature are generally similar to those noted in clinical trials with diarrhea being the most frequently reported. The safety databases from TESS, FDA SRS/AERS, WHO, and DAWN did not reveal any specific trend or signal detected with the use of lansoprazole. A safety update submitted in November 2008 for single-ingredient lansoprazole did not reveal any new or unexpected serious safety issues. This reviewer checked FDA's electronic files (DARRTS) for any active safety issues on lansoprazole. There is an entry and an ongoing discussion regarding long-term PPI therapy (>1 year) and risk of hip fractures; however, this should not be a concern for the OTC use of lansoprazole 15 mg if used according to the proposed label. The reviewers in the Division of Adverse Events 1 and DGP were also asked about any active safety issues regarding drug; there are no other issues at this time.

Lansoprazole has been marketed with a well-characterized safety profile for prescription use in the United States for over 13 years at doses up to 90 mg twice a day. The extensive postmarketing data, previous clinical trials, literature review, and adverse events analysis from the clinical efficacy studies conducted by the sponsor do not raise any new safety concerns and establish the safety of lansoprazole 15 mg for OTC use for the treatment of frequent heartburn for 14 days.

1.3.4 Dosing Regimen and Administration

The proposed indication is for the treatment of frequent heartburn occurring two or more days a week in adults 18 years of age and older. The dosing regimen is one lansoprazole 15 mg capsule once a day (every 24 hours) for 14 days; the treatment course maybe repeated every 4 months if necessary.

Prescription labeling recommends considering dose reduction in patients with severe liver disease because, in patients with various degrees of chronic hepatic disease, the mean plasma half-life of lansoprazole was prolonged and the mean AUC was increased (up to 500%) at steady state compared to healthy subjects. Therefore, the Directions and Warnings sections of the

2 Cases classified as serious may also contain non-serious events.

proposed lansoprazole OTC label should include the following statement, "Consumers with liver disease, ask a doctor", or similar language.

1.3.5 Drug-Drug Interactions

There are no new drug-drug interactions evaluated with this application. There is also no new significant information on drug interactions that warrants any changes in the lansoprazole label. The following drug interactions are addressed in the current lansoprazole prescription label:

- Lansoprazole should not be co-administered with atazanavir.
- Lansoprazole is metabolized through the cytochrome P450 system; studies have shown that it does not have clinically significant interactions with other drugs metabolized through various cytochrome P450 isozymes, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving PPIs (including lansoprazole), and warfarin concomitantly; therefore, patients may need to be monitored for increases in INR and prothrombin time.
- When lansoprazole was concomitantly with theophylline, a minor increase (10%) in the clearance of theophylline was seen, additional titration of theophylline dosage may be required when lansoprazole is started or stopped.
- It is also theoretically possible that lansoprazole may also interfere with the absorption of other drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

The proposed OTC label warns consumers not to use the product if there is allergic reaction to lansoprazole, and to ask a doctor or pharmacist before use if taking any of the following drugs: warfarin, prescription antifungal or anti-yeast medicines, [redacted] digoxin, theophylline, tacrolimus, atazanavir [redacted] b(4)

[redacted] Tacrolimus (an immunosuppressant) was not specifically listed in the Drug Interactions section of the lansoprazole prescription label; however, both drugs are metabolized via the hepatic cytochrome P-450 (CYP)3A4. In certain patients, tacrolimus whole blood concentrations may be more dramatically increased which may lead to nephrotoxicity or other side effects (see section 8.2). It is important that consumers who are on tacrolimus ask their physicians before taking lansoprazole.

1.3.6 Special Populations

No new information regarding special populations was submitted with this NDA. There are no new significant data regarding other patient populations and the effects of gender, race, or age on safety. Lansoprazole is currently listed as Pregnancy Category B. The proposed OTC label include appropriate warnings to certain consumers such as pregnant and breastfeeding women. Patients with severe liver disease should consult a doctor before use.

Pediatrics
Pediatric patients were not evaluated in this NDA. No new significant data were submitted by the sponsor regarding this population for the proposed indication.

The safety and effectiveness of lansoprazole for OTC use for the indication of frequent heartburn have not been established for pediatric patients (<18 years old). For patients less than 18 years old, it is more appropriate to use lansoprazole under the supervision of a physician for proper diagnosis and treatment. The sponsor is requesting a waiver to conduct pediatric studies; this request should be granted. Granting this waiver is consistent with the Agency's decision to waive pediatric studies for another drug (omeprazole) in the same class, and currently marketed for OTC use for the same indication.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Lansoprazole (Prevacid®) is a proton-pump inhibitor (PPI) initially approved as a prescription product on May 10, 1995 for the treatment of acid-related gastrointestinal disorders (see Table 1 for indication and dosing). It is indicated in both adults and children as young as one year of age. It may be used as a single-ingredient product or in combination with amoxicillin and/or clarithromycin for the treatment of H. pylori infection. Oral lansoprazole is currently available for prescription use in 15 and 30 mg strengths in the following delayed-release formulations: capsules, oral suspension in unit dose packets, and solutab (orally disintegrating tablets). There is an injection formulation available as 30 mg dosage strength. Prevacid 15 mg is also co-packaged with 375 or 500 mg naproxen tablets. Currently, lansoprazole is sold as a prescription only product worldwide. At the time of this NDA submission, according to the sponsor, it has been approved, [ ] for OTC sale in Sweden. b(4)

There are currently no OTC indications for lansoprazole use in the United States. The sponsor of this application, Novartis Consumer Healthcare, Inc. (NCH) is seeking approval to market lansoprazole delayed release capsules 15 mg for OTC use for the indication of *frequent* heartburn (occurring two or more days per week) in adults 18 years of age and older. Omeprazole 20 mg, the first PPI marketed for OTC use, has the same indication and once-daily, 14-day dosing.

Table 1: Lansoprazole (Prevacid®) Prescription Indications, Dosage and Administration

Indication	Recommended Dose	Frequency
Duodenal Ulcers		
Short-Term Treatment	15 mg	Once daily for 4 weeks
Maintenance of Healed	15 mg	Once daily
H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence		
Triple Therapy:		
PREVACID	30 mg	Twice daily (q12h) for 10 or 14 days
Amoxicillin	1 gram	Twice daily (q12h) for 10 or 14 days
Clarithromycin	500 mg	Twice daily (q12h) for 10 or 14 days
Dual Therapy:		
PREVACID	30 mg	Three times daily (q8h) for 14 days
Amoxicillin	1 gram	Three times daily (q8h) for 14 days
Benign Gastric Ulcer		
Short-Term Treatment	30 mg	Once daily for up to 8 weeks
NSAID-associated Gastric Ulcer		
Healing	30 mg	Once daily for 8 weeks
Risk Reduction	15 mg	Once daily for up to 12 weeks

Indication	Recommended Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Short-Term Treatment of Symptomatic GERD	15 mg	Once daily for up to 8 weeks
Short-Term Treatment of Erosive Esophagitis	30 mg	Once daily for up to 8 weeks
Pediatric (1 to 11 years of age)		
Short-Term Treatment of Symptomatic GERD and Short-Term Treatment of Erosive Esophagitis		
≤ 30 kg	15 mg	Once daily for up to 12 weeks
> 30 kg	30 mg	Once daily for up to 12 weeks
(12 to 17 years of age) Short-Term Treatment of Symptomatic GERD		
Nonerosive GERD	15 mg	Once daily for up to 8 weeks
Erosive Esophagitis	30 mg	Once daily for up to 8 weeks
Maintenance of Healing of Erosive Esophagitis	**15 mg**	**Once daily**
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	**60 mg (starting dose)**	**Once daily (twice daily dosing have been administered)**

Adapted from lansoprazole prescription label, PDR Electronic Library 8/2008 (http://www.thomsonhc.com/pdrel/librarian)

2.2 Currently Available Treatment for Indications

There are other currently available medical treatments for the sponsor's proposed OTC indication of *frequent* heartburn. These are the currently marketed OTC PPI, omeprazole magnesium (Prilosec OTC®) and omeprazole delayed release tablets, 20 mg. Omeprazole OTC is currently marketed for use in adults 18 years of age and older, used once a day for 14 days; this treatment course maybe repeated every 4 months if necessary.

There are other OTC products available for the treatment of other acid-related gastrointestinal disorders such as episodic heartburn. These include H_2-receptor antagonists (ranitidine, cimetidine, famotidine and nizatidine), and antacids (aluminum and/or magnesium hydroxide, calcium bicarbonate, sodium bicarbonate).

2.3 Availability of Proposed Active Ingredient in the United States

Lansoprazole is currently only marketed as a prescription product and is only available under the brand name Prevacid®. It is available in the following 15 and 30 mg strength delayed-release formulations: capsules, oral suspension in unit dose packets, and solutab (orally disintegrating tablets). There is an injection formulation available as 30 mg dosage strength.

2.4 Important Issues with Pharmacologically Related Products

Due to the profound and long lasting inhibition of gastric acid secretion from proton pump inhibitors (PPIs), it is theoretically possible that these drugs may interfere with the absorption of certain drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, iron salts and digoxin).

The systemic concentration of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, is decreased when concomitantly administered with PPIs. This may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole or other PPIs should not be co-administered with atazanavir.

There have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin may need to be monitored for increases in INR and prothrombin time.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the PPIs was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, PPIs should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with lansoprazole and there was no evidence of a change in the efficacy of lansoprazole.[3]

PPIs are also known to inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (e.g., disulfiram, benzodiazepines). Individual patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PPIs.

These important issues with pharmacologically related products are reflected in the current prescribing information and partly in the proposed OTC label (for the most significant issues) for lansoprazole.

2.5 Presubmission Regulatory Activity

The marketing of Prevacid® (TAP Pharmaceutical Products) was originally approved by the FDA for prescription use since 1995 for the treatment of gastrointestinal acid-related disorders. It is approved for the management of duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), erosive esophagitis, and pathological hypersecretory conditions. There are currently no OTC indications for lansoprazole use in the United States. The sponsor is proposing for the OTC use of lansoprazole 15 mg for the treatment of frequent heartburn (occurring 2 or more days a week). Another product in the same drug class, omeprazole delayed release tablet 20 mg (Prilosec OTC®), was approved for OTC use for the treatment of *frequent* heartburn on June 20, 2003. The sponsor reports that several studies support the efficacy of the lansoprazole 15 mg for the treatment of heartburn symptoms and strongly suggest that lansoprazole will be an ideal candidate for the treatment of frequent heartburn.

3 Prevacid Rx Label, PDR Electronic Library (http://www.thomsonhc.com/pdrel/librarian) accessed on 8/12/08.

Novartis Consumer Health, Inc. (NCH) has entered into an agreement with Takeda Abbott Pharmaceuticals (TAP), the holder of NDA 20-406 and IND 30,159 (Prevacid® Delayed-Release Capsules), granting NCH full right of reference of their data contained in these submissions in support of all NCH's applications related to the OTC use of Prevacid®.

A pre-IND meeting was held on April 6, 2006 between NCH and FDA to discuss the clinical development program for the proposed OTC indication, design of the pivotal clinical trials, and draft labeling. On May 5, 2006, NCH opened IND 74,256 for lansoprazole delayed-release capsules for OTC use. The IND application included the protocols for two identical clinical studies to demonstrate that repeated daily doses of 15 mg of lansoprazole once a day are effective in increasing the proportion of days with no heartburn during 14 days (24-hour days) of treatment as compared to placebo. (See meeting minutes entered in DARRTS.)

On July 27, 2006, the NCH requested a special clinical protocol assessment (SPA) for study PRSW-GN-305: A phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group trial of fourteen day treatment with lansoprazole 15 mg and lansoprazole 30 mg once a day in frequent nighttime heartburn. Responses to the sponsor's questions and comments can be found in DARRTS entered on September 8, 2006.

[b(4)

On March 17, 2008, a pre-NDA meeting was held to discuss NCH plans to submit a 505(b)(1) NDA for OTC use of Prevacid delayed-release capsules for the treatment of frequent heartburn [ ] On July 16, 2008, FDA received this 505(b)(1) application, NDA 22-327, seeking the OTC use of Prevacid delayed release capsules for the indication of frequent heartburn. b(4)

2.6 Other Relevant Background Information

Lansoprazole is currently the only PPI approved for both healing and risk reduction of non-steroidal anti-inflammatory drug (NSAID) associated gastric ulcers (prescription indications).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The proposed product, Prevacid 24HR® delayed-release capsule, contains lansoprazole 15 mg as the active drug substance; this has been previously approved for prescription use (Prevacid®) under TAP's NDA 20-406. The capsule has a pink body and teal (blue-green) cap with a black tamper evident band containing white to pale brownish white granules. The capsule is printed

with [ ] on the teal (blue-green) cap. NCH makes reference to the applications from the original NDA 20-406 submission for the CMC information. See Chemistry review for details. Microbiology review was not necessary for this application. b(4)
Table 2 lists the product's composition.

Table 2: Lansoprazole AG-1749 Granule Composition

Component [ ]	Reference to quality standard	Function	mg/capsule
Lansoprazole	USP	Active substance	15.0
Magnesium carbonate	USP	[	
Sugar spheres	NF		
Sucrose, [	NF		
[starch	NF		
Low-substituted hydroxypropyl cellulose, LH-T	NF		
Hydroxypropyl cellulose, L	NF		
[	USP		
Methacrylic acid copolymer	NF		
Polyethylene glycol [	NF		
Titanium dioxide	USP		
Polysorbate 80	NF		
Talc	USP		
[	USP		
Talc	USP		
Colloidal silicon dioxide	NF		]

b(4)
b(4)
b(4)
b(4)

3.2 Animal Pharmacology/Toxicology

There are no new animal data or toxicology studies submitted with this NDA, nor did FDA request any new preclinical studies. The sponsor refers to the information in the previously submitted NDA 20-406.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data to support this application include the three clinical efficacy studies (PRSW-GN-301, PRSW-GN-302 and PRSW-GN-305) conducted by the sponsor. These were all large placebo-controlled randomized studies in a total of 1,986 subjects. These studies evaluated the efficacy of lansoprazole 15 mg once daily for 14 days for the treatment of frequent

heartburn. Study 301 and Study 302 had the same efficacy endpoint: the proportion of 24-hr days with no heartburn over 14 days. The primary endpoint for Study 305 was the proportion of nighttimes with no heartburn over 14 days. In addition, Study 305 investigated the efficacy of lansoprazole 30 mg once daily for 14 days on an exploratory basis for the treatment of frequent heartburn. Additional sources of safety data, including the post-marketing safety surveillance data and literature search for lansoprazole, are also provided to support the safety of lansoprazole 15 mg in an OTC population.

4.2 Tables of Clinical Studies

Table 3: Summary of Placebo-Controlled Phase III Clinical Studies

Trial	*Objective*	*Trial Design*	*Population*	*Treatment*	*Efficacy endpoints*
PRSW-GN-301 35 sites, US	Efficacy/ safety in subjects with frequent heartburn (HB)	Multicenter, double-blind, randomized, parallel group, placebo-controlled study in an OTC population of frequent HB (≥2 episodes/wk)	Planned: 576 Total: 564 69.1% Caucasian 9.9% Black 13.8% Hispanic 3.5% Asian 3.5% Other	Randomized 1:1 to Lansoprazole 15 mg or Placebo OD before breakfast 7 day Placebo Run-in period, ↓ 14 day Placebo-controlled treatment period, ↓ 7 day Placebo ff-up period	<u>Primary:</u> =proportion of 24-hr days with no HB over 14 days <u>Secondary:</u> =proportion of *nighttimes* with no HB over 14 days =proportion of days with no HB over Days 1-2 =proportion of subjects with no HB on Day 1
PRSW-GN-302 37 sites, US			Planned: 576 Total: 570 74.9% Caucasian 11.2% Black 12.8% Hispanic 0.4% Asian 0.7% Other		
PRSW-GN-305 61 sites, US		Multicenter, double-blind, randomized, parallel group, placebo- controlled study in an OTC population of frequent HB (≥2 episodes/wk during *nighttime*)	Planned: 864 Total: 852 66.9% Caucasian, 13.8% Black 14.6% Hispanic 3.6% Asian 1.1% Other	Randomized 1:1:1 to Lansoprazole 15 mg or Lansoprazole 30 mg or Placebo OD before breakfast 7 day Placebo Run-in period ↓ 14 day Placebo-controlled treatment period ↓ 7 day placebo ff-up period	<u>Primary:</u> =proportion of *nighttimes* with no HB over 14 days <u>Secondary:</u> =proportion of 24-hr days with no HB over 14 days =proportion of subjects with no HB on Day 1

HB-heartburn

4.3 Review Strategy

This review will evaluate the safety of lansoprazole 15 mg for OTC use by reviewing

- the adverse events data from the Phase III clinical efficacy studies conducted by the sponsor for the proposed indication
- the postmarketing safety data for lansoprazole since its initial approval in 1995

The efficacy portion of this NDA review will be evaluated by the Division of Gastroenterology Products (DGP). A reviewer from the Division of Nonprescription Regulation Development (DNRD) will be reviewing the proposed lansoprazole OTC label in detail.

This safety review includes an analysis of adverse events including information from:

- TAP's Postmarketing Drug Safety Database
- Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS)
- World Health Organization (WHO) International Drug Monitoring Program
- Toxic Exposure Surveillance System (TESS) database maintained by the American Association of Poison Control Centers (AAPCC)
- Drug Abuse Warning Network (DAWN) database
- Medical literature

4.4 Data Quality and Integrity

A DSI inspection was requested for the following studies and corresponding clinical sites:

- 301 site no. 124
- 302 site no. 215
- 305 site no. 548

Final results for Studies 302 and 305 and preliminary inspection results for Study 301 were acceptable at the time this NDA review was written.

4.5 Compliance with Good Clinical Practices

The sponsor states that the three studies were conducted according to the ethical principles of the Declaration of Helsinki. The study and any amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center. Informed consent was obtained from each subject in writing at Visit 1 (Screening). The study was described by a study coordinator and/or the investigator, who answered any questions, and written information was also provided.

4.6 Financial Disclosures

An FDA form 3454 was submitted certifying that NCH has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the

investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). There were no financial disclosures that would cast doubt on the findings of the studies.

5 CLINICAL PHARMACOLOGY

Lansoprazole 15 and 30 mg capsules were used in the Phase III development program for the proposed OTC indication. A capsule formulation will be used for OTC marketing.

5.1 Pharmacokinetics

There are no new clinical pharmacology data included in this submission. The sponsor refers to the information submitted to prescription lansoprazole to support this NDA. The following clinical pharmacology information is reflected in the prescribing information for lansoprazole.

Prevacid® delayed-release capsules contain an enteric-coated granule formulation of lansoprazole. Absorption begins only after the granules leave the stomach, and is rapid with the mean C_{max} occurring approximately 1.7 hours after oral dosing; the absolute bioavailability is over 80%. In healthy subjects, the mean (±SD) plasma half-life was 1.5 (±1.0) hours. Both the C_{max} and AUC are diminished by about 50% to 70% if lansoprazole is given 30 minutes after food, compared to the fasting condition. There is no significant food effect if given before meals.

Lansoprazole is 97% bound to plasma proteins. It is extensively metabolized in the liver; two metabolites have been identified in measurable quantities in the plasma, the hydroxylated sulfinyl and sulfone derivatives of lansoprazole. These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by blocking the proton pump (H^+/K^+-ATPase enzyme system) at the secretory surface of the gastric parietal cell. The two active species are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours; the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

Following single-dose oral administration, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ^{14}C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of its metabolites. Lansoprazole does not accumulate and its pharmacokinetics (PK) are unaltered by multiple dosing.

Drug and Substance Interactions
Lansoprazole causes long-lasting inhibition of gastric acid secretion. It substantially decreases the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption. This may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, lansoprazole or other PPIs should not be co-administered with atazanavir.

Lansoprazole is metabolized through the cytochrome P450 system, specifically through the

CYP3A and CYP2C19 isozymes. Studies have shown that it does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects.

When lansoprazole was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the latter's clearance was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels.

In a study of healthy subjects neither the PK of warfarin enantiomers nor prothrombin time (PT) were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and PT in patients receiving PPIs, including lansoprazole, and warfarin concomitantly. Increases in INR and PT may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and PT.

In an open-label, single-arm, eight-day, PK study of 28 adult rheumatoid arthritis patients (who required the chronic use of 7.5 to 15 mg of methotrexate given weekly), administration of 7 days of naproxen 500 mg BID and lansoprazole 30 mg daily had no effect on the PK of methotrexate and 7-hydroxymethotrexate. While this study was not designed to assess the safety of this combination of drugs, no major adverse events were noted.

In a single-dose crossover study examining lansoprazole 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the PPIs was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. In clinical trials, antacids were administered concomitantly with lansoprazole and there was no evidence of a change in the efficacy of lansoprazole.

Geriatrics
The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole; peak plasma levels were not increased. No dosage adjustment is necessary in the elderly.

Pediatrics
The PK of lansoprazole were studied in pediatric patients with GERD aged 1 to 11 years and 12 to 17 years in two separate clinical studies. In children aged 1 to 11 years, lansoprazole was dosed 15 mg daily for subjects weighing ≤30 kg and 30 mg daily for subjects weighing >30 kg. In adolescent subjects aged 12 to 17 years, subjects were randomized to receive lansoprazole at 15 mg or 30 mg daily. Overall, lansoprazole PK in pediatric patients aged 1 to 17 years were similar to those observed in healthy adult subjects.

Gender
In a study comparing 12 male and 6 female human subjects who received lansoprazole, no gender differences were found in pharmacokinetics and intragastric pH results.

Renal Insufficiency
In patients with severe renal insufficiency, plasma protein binding is decreased by 1-1.5% after administration of 60 mg of lansoprazole. These patients had a shortened elimination half-life and decreased total AUC (free and bound). The AUC for free lansoprazole in plasma was not related to the degree of renal impairment; and the Cmax and Tmax were not different than those with normal renal function. No dosage adjustment is necessary in patients with renal insufficiency.

Hepatic Insufficiency
In patients with various degrees of chronic hepatic disease, the mean plasma half-life of lansoprazole was prolonged from 1.5 hours to 3.2-7.2 hours. An increase in the mean AUC of up to 500% was observed at steady state in hepatically-impaired patients compared to healthy subjects. Dose reduction in patients with severe hepatic disease should be considered.

Medical Officer Comments: Under the Dosage and Administration section of the prescription label for lansoprazole, it is stated that renal insufficiency patients and geriatric patients do not require dosage adjustment. However, dose adjustment should be considered in patients with severe liver disease; therefore, it is important that this warning for patients with liver disease be reflected in the OTC label as well.

Race
The pooled mean PK parameters of lansoprazole from 12 Phase 1 (U.S.) studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of lansoprazole in Asian subjects were approximately twice those seen in pooled U.S. data; however, the inter-individual variability was high. The C_{max} values were comparable. Prescription labeling does not recommend a dosage adjustment for Asian patients.

5.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this NDA. The following information is included in the prescription label for lansoprazole.

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by the specific inhibition of the (H+,K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. Lansoprazole does not exhibit anticholinergic or histamine type-2 antagonist activity.

5.3 Exposure-Response Relationships

There is no new exposure-response relationship information submitted with this application.

6 INTEGRATED REVIEW OF EFFICACY

The efficacy of lansoprazole 15 mg in adults aged 18 years and older for the treatment of frequent heartburn is supported by three placebo-controlled trials (PRSW-GN-301, PRSW-GN-302 and PRSW-GN-305) conducted by the sponsor. The efficacy of lansoprazole 30 mg once daily for 14 days was also investigated in Study 305 on an exploratory basis for the treatment of frequent heartburn. A total of 1,986 subjects were enrolled; 1,138 subjects were treated with lansoprazole (861 received lansoprazole 15 mg, 277 received lansoprazole 30 mg) and 848 were treated with placebo. These studies had basically similar designs, see Figure 1 below.

Figure 1: General Study Design of the Three Efficacy Studies

Screening / Washout	Run-in	Baseline	End of Study	Follow-up
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Day –14 to -7	Day -8	Day 1	Day 16	Day 24
Heartburn medication washout	Single-blind placebo	Start of double-blind treatment	End of double-blind treatment; start of single-blind placebo follow-up	End of single-blind placebo follow-up
1 week	1 week	----------2 weeks----------		1 week

The design and objectives of studies PRSW-GN-301 and PRSW-GN-302 were identical. The objective was to demonstrate that lansoprazole 15 mg once daily dosed in the morning is superior to placebo in reducing the frequency of heartburn episodes during the 14-day double-blind treatment period. The primary efficacy parameter was the proportion of heartburn free 24-hour days during the 14-day treatment period. The secondary efficacy parameters were the proportion of heartburn free nighttimes, the proportion of heartburn free 24-hour days during the first 2 days of double-blind treatment, and the proportion of subjects with no heartburn on Day 1.

The third study, PRSW-GN-305, was also conducted in a population of frequent heartburn sufferers utilizing the same study design employed in Studies 301 and 302. However, all subjects in Study 305 were also required to have a history of frequent heartburn during *nighttimes*. The primary efficacy parameter was the proportion of heartburn free *nighttimes* during the 14-day treatment period. The secondary efficacy parameters were the proportion of heartburn free days, the proportion of heartburn free 24-hour days during the first 2 days of double-blind treatment, and the proportion of subjects with no heartburn on Day 1.

The efficacy review of this NDA will be addressed by the Division of Gastroenterology Products (DGP), review entered in DFS.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This safety review focuses on the use of single-ingredient lansoprazole 15 mg for 14 days, the proposed treatment regimen for OTC use. The information for the 30 mg dose was included in the review to provide additional safety information. The safety of higher lansoprazole doses and/or its use for longer that 14 days (prescription use) will not be addressed in detail this review. Information regarding the safety of lansoprazole for the prescription use has been previously submitted to the approved prescription NDAs for this drug. The clinical data utilized in this review of safety to support the OTC use of lansoprazole include:

- Safety data from the three clinical trials conducted by NCH (301, 302, and 305)
- Analysis of all postmarketing adverse events from the global postmarketing AE reports received by TAP (May 10, 1995 to Sep 30, 2007)
- A report summarizing adverse event reporting to the FDA from the Spontaneous Reporting System (SRS)(1969 to October 1997) and the Adverse Event Reporting System (AERS) (November 1997 to June 2007)
- Analysis of reports to the American Association of Poison Control Centers' (AAPCC) Toxic Exposure Surveillance System (TESS) database (2000-2006)
- A report of the Drug Abuse Warning Reports (DAWN) for lansoprazole (January 2003 to April 2007)
- A report summarizing adverse event report to the World Health Organization's (WHO) International Drug Monitoring Program (October 1993 to July 2008)
- A review of medical literature relevant to the safety of lansoprazole (January 1988 to December 2007)
- Current lansoprazole prescription labels (U.S.)
- Proposed lansoprazole OTC labels including package inserts

The safety data from the three clinical studies submitted by NCH for the indication of frequent heartburn will be discussed in detail in this review. All subjects exposed to at least one dose of study treatment will be included in the safety assessment of lansoprazole 15 mg product for OTC use. Safety information from the prescription label and postmarketing will also be included and discussed in the appropriate sections of this NDA review.

7.1.1 Deaths

During the clinical development of lansoprazole for OTC use, there were two reports of death from the controlled trials, 1 each from the lansoprazole 15 mg and placebo group. Neither death was thought to be related to the administration of study medication.

- Subject 113/1273 (Study PRSW-GN-301) is a 90 year old male in the lansoprazole 15 mg group who experienced angina pectoris on Day 4 during the follow-up phase. On Day 7, his physician decided to perform a heart catheterization, the subject subsequently went into ventricular fibrillation, experienced a cardiac arrest, and died. He had history of

prostate cancer (1991), hypertension (from 1985), and bilateral hip replacement (1980 and 2000). Concomitant medications had included hydrochlorothiazide (25 mg) and aspirin (81 mg).

- Subject 217/2489 (Study PRSW-GN-302) is a 41-year old male in the placebo group who had a cerebrovascular accident on Day 11 during the treatment phase. The subject had a long standing history of hypertension and was reported to have history of non-compliance with antihypertensive treatment. Subject had history of HIV+ (1986) and blurred vision.

7.1.2 Other Serious Adverse Events

Tables 4 and 5 list all serious adverse events (SAEs) from the clinical trials conducted by NCH.

Table 4: Serious Adverse Events (Excluding Deaths): Treatment Phase

	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg
No. of subjects	861 (100)	848 (100)	277 (100)
No. of subjects in any SOC - N (%)	4 (0.5)	2 (0.2)	1 (0.4)
SOC or Preferred term			
Gastrointestinal disorders SOC	0 (0.0)	1 (0.1)	0 (0.0)
Gastrooesophageal reflux disease		1 (0.1)	
Infections and infestations SOC	1 (0.1)	0 (0.0)	0 (0.0)
Pneumonia bacterial	1 (0.1)		
Injury, poisoning and procedural complications SOC	1 (0.1)	0 (0.0)	0 (0.0)
Cervical vertebral fracture	1 (0.1)		
Fall	1 (0.1)		
Jaw fracture	1 (0.1)		
Joint dislocation	1 (0.1)		
Scapula fracture	1 (0.1)		
Neoplasm benign, malignant and unspecified (incl. cysts and polyps) SOC	1 (0.1)	0 (0.0)	0 (0.0)
Breast cancer	1 (0.1)		
Nervous system disorders SOC	1 (0.1)	0 (0.0)	0 (0.0)
Convulsion	1 (0.1)		
Psychiatric disorders SOC	0 (0.0)	1 (0.1)	1 (0.4)
Bipolar disorder		1 (0.1)	
Panic attack			1 (0.4)

Sponsor's table CTD 2.7.4 p.46

The following SAEs were recorded for each group during the treatment phase: lansoprazole 15 mg - bacterial pneumonia, injuries resulting from a fall, breast cancer, and convulsion in 4 subjects; lansoprazole 30 mg - panic attack; placebo group - panic attack and worsening of GERD in 1 subject.

Table 5: Serious Adverse Events (Excluding Deaths): Follow-up Phase

	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg
No. of subjects	861 (100)	848 (100)	277 (100)
No. of subjects in any SOC - N (%)	3 (0.3)	0 (0.0)	1 (0.4)
SOC or Preferred term			
Gastrointestinal disorders SOC	2 (0.2)	0 (0.0)	0 (0.0)
Abdominal pain lower	1 (0.1)		
Diarrhoea	1 (0.1)		
Vomiting	1 (0.1)		
Neoplasm benign, malignant and unspecified (incl. cysts and polyps) SOC	2 (0.2)	0 (0.0)	0 (0.0)
Colon cancer	1 (0.1)		
Degeneration of uterine fibroid	1 (0.1)		
Nervous system disorders SOC	0 (0.0)	0 (0.0)	1 (0.4)
Syncope			1 (0.4)
Surgical and medical procedures SOC	1 (0.1)	0 (0.0)	0 (0.0)
Mastectomy	1 (0.1)		

Sponsor's table CTD 2.7.4 p.47

During the placebo follow-up period, the following SAEs were reported for each group: lansoprazole 15 mg – abdominal pain, diarrhea, vomiting, colon cancer, uterine fibroid, and mastectomy in 3 patients; lansoprazole 30 mg - syncope in 1 subject; placebo-none.

None of the serious adverse events that occurred during both phases of the studies appear to be related to study medication and there appears to be no relationship between the dose or duration of therapy and SAEs reported.

7.1.3 Dropouts and Other Significant Adverse Events

Regardless of severity or seriousness of the AEs, the following subjects in each group discontinued from study participation in the treatment phase: lansoprazole 15 mg - 8 (0.9%), lansoprazole 30 mg - 4 (1.4%), and placebo -7 (0.8%) (Table 6). Of the 17 AEs reported for the lansoprazole 15 mg group, 4 (diarrhea-2, abdominal pain-1 and abdominal pain -1) could be plausibly related to study drug administration. In the lansoprazole 30 mg group, 4 of 5 AE terms could be plausibly related to study drug administration: diarrhea-1, nausea-1, rash-2 (Table 7). During the follow-up phase, 2 subjects in the 15 mg lansoprazole group reported 5 AEs and discontinued from the study. One was the death (discussed in section 7.1.1) attributed to ventricular fibrillation and another was a case colon cancer. No discontinuation was reported for the other treatment groups. Both cases were considered not related to the study drug.

Table 6: Overall Subject Disposition: End of Treatment phase and Overall N (%)

Total number of subjects	Lansoprazole 15 mg		Placebo		Lansoprazole 30 mg	
Randomized	861 (100)		848 (100)		277 (100)	
Treated	861 (100)		848 (100)		277 (100)	
	End of Rx	Overall	End of Rx	Overall	End of Rx	Overall
Completed	831 (96.5)	823 (95.6)	817 (96.3)	812 (95.8)	265 (95.7)	264 (95.3)
Discontinued	30 (3.5)	38 (4.4)	31 (3.7)	36 (4.2)	12 (4.3)	13 (4.7)
Main reason for discontinuation						
Adverse event(s)	6 (0.7)	8 (0.9)	6 (0.7)	7 (0.8)	4 (1.4)	4 (1.4)
Protocol deviation	2 (0.2)	2 (0.2)	3 (0.4)	4 (0.5)	0 (0.0)	0 (0.0)
Subject withdrew consent	9 (1.0)	11 (1.3)	14 (1.7)	15 (1.8)	8 (2.9)	8 (2.9)
Lost to follow-up	9 (1.0)	12 (1.4)	6 (0.7)	8 (0.9)	0 (0.0)	1 (0.4)
Administrative problems	3 (0.3)	3 (0.3)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Lack of efficacy	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
The percent basis is the number of subjects randomized for a given treatment.						

Sponsor's table Module 5.3.5.3 p. 37

The overall discontinuation rates do not appear to be markedly different for both the lansoprazole groups and placebo, and there does not appear to be a relationship between dose and subjects who discontinued.

Table 7: Discontinuations for Adverse Events: Treatment Phase

	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg
No. of subjects	861 (100)	848 (100)	277 (100)
No. of subjects in any SOC - N (%)	8 (0.9)	4 (0.5)	4 (1.4)
SOC or Preferred term			
Gastrointestinal disorders	4 (0.5)	2 (0.2)	2 (0.7)
Abdominal pain	1 (0.1)		
Abdominal pain upper	1 (0.1)		
Diarrhoea	2 (0.2)	1 (0.1)	1 (0.4)
Gastrooesophageal reflux disease		1 (0.1)	
Nausea			1 (0.4)
Rectal haemorrhage	1 (0.1)		
Vomiting	1 (0.1)		
General disorders and administration site conditions	0 (0.0)	1 (0.1)	0 (0.0)
Oedema		1 (0.1)	
Infections and infestations	1 (0.1)	0 (0.0)	0 (0.0)
Pneumonia bacterial	1 (0.1)		
Injury, poisoning and procedural complications	1 (0.1)	0 (0.0)	0 (0.0)
Cervical vertebral fracture	1 (0.1)		
Fall	1 (0.1)		
Jaw fracture	1 (0.1)		
Joint dislocation	1 (0.1)		
Scapula fracture	1 (0.1)		
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.1)	0 (0.0)
Pain in extremity		1 (0.1)	
Nervous system disorders	3 (0.3)		1 (0.4)
Convulsion	1 (0.1)		
Dizziness	1 (0.1)		
Headache	2 (0.2)		1 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (0.1)	0 (0.0)	0 (0.0)
Pharyngeal oedema	1 (0.1)		
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	2 (0.7)
Rash			1 (0.4)
Rash generalised			1 (0.4)
Vascular disorders	0 (0.0)	1 (0.1)	0 (0.0)
Hot flush		1 (0.1)	

Sponsor's table Module 5.3.5.3 p.58

7.1.4 Other Search Strategies

There were no other search strategies conducted for this NDA.

7.1.5 Common Adverse Events

The following sections of the review focuses on establishing the common adverse event profile for lansoprazole 15 mg using data from the three clinical trials conducted for the proposed OTC indication and from the trials previously conducted for the prescription indications.

7.1.5.1 Eliciting adverse events data in the development program

AEs for the clinical studies were identified and recorded through a combination of Case Report Form (CRF) data collected during subject visits and subject diaries completed between visits.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor used the Medical Dictionary for Regulatory Activities (MedDRA) to describe all AEs during the clinical trials. The verbatim terms were mapped to MedDRA v9.0; this version was utilized throughout the clinical development program. However, for the post-marketing datasets, MedDRA v10.1 was utilized.

The frequency of AEs is presented by System Organ Class (SOC) and by Preferred Terms (PTs), and was categorized depending on severity, possible study drug association, seriousness, and cause for withdrawal from the study. The severity of an AE was determined by the investigator and recorded on the AE report in the subject's CRF. Tables for the overall AE frequencies were also prepared for HLGT and HLT. The data for the subjects receiving the 30 mg dose were presented separately but all AEs for the 15 mg lansoprazole and placebo treatment groups, respectively, have been merged by treatment.

AE frequencies are for the treatment-emergent AEs using the number of treated subjects (the safety analysis population) as the denominator. In cases where a subject reported the same AE more than once, the AE was counted only once for the relevant table. In general, the occurrence regarded as most serious or most severe was used.

The adverse event categorization and preferred terms used in the clinical studies were appropriate.

7.1.5.3 Incidence of common adverse events

In the clinical trials conducted for the frequent heartburn indication, the most frequently observed AE occurring in 0.5% or more of subjects in any treatment group during the treatment phase, regardless of relationship to study medication was diarrhea; the frequency was higher compared to placebo (1.7%, 15/861 vs. 0.4%, 3/848), see Table 8. In the follow-up phase, the most frequently reported AEs regardless of relationship to study medication that had higher rates observed for the 15 mg treatment group compared to placebo were: diarrhea (0.9%, 8/861 vs. 0%), URI (0.7%, 6/861 vs. 0%), and nasopharyngitis (0.6%, 5/861 vs. 0%), see Table 9.

In Phase 2 or Phase 3 clinical trials conducted worldwide involving various dosages and durations of treatment for the prescription indications, over 10,000 patients have been treated with lansoprazole (Prevacid®). The following adverse events were reported by the treating physician to have a possible or probable relationship to the drug in 1% or more of lansoprazole - treated patients and occurred at a greater rate than placebo-treated patients (Table 11): abdominal pain, constipation, diarrhea and nausea.[4]

7.1.5.4 Common adverse event tables

Regardless of relationship to study medication, the most frequently reported AEs were:

4 Prevacid Prescription Label, Adverse Reactions section (http://www.pdr.net) accessed 11-24-08.

- Treatment phase: diarrhea in the 15 mg and 30 mg treatment groups compared to placebo, 1.7% and 1.4% vs. 0.4%, respectively. Headache was also seen at greater than 1% incidence but was more common on placebo than 15 and 30 mg lansoprazole, 1.4% vs. 1.2% vs. 0.7% respectively (Table 8).
- Follow-up phase: diarrhea in the 15 mg and 30 mg treatment groups compared to placebo, 0.9% and 0.4% vs. 0% respectively, and URI (0.7% and 0.4% vs. 0%) (Table 9).

Table 8: Most Frequent Adverse Events (≥ 0.5%): Treatment Phase

SOC Abbrev.	Preferred term	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg
No of subjects		861 (100)	848 (100)	277 (100)
No with any AE(s) - N (%)		88 (10.2)	70 (8.3)	31 (11.2)
Gastr	Diarrhoea	15 (1.7)	3 (0.4)	4 (1.4)
Nerv	Headache	10 (1.2)	12 (1.4)	2 (0.7)
Gastr	Constipation	2 (0.2)	4 (0.5)	3 (1.1)
Gastr	Nausea	6 (0.7)	6 (0.7)	3 (1.1)
Inj&P	Overdose		5 (0.6)	3 (1.1)
Infec	Nasopharyngitis	9 (1.0)	6 (0.7)	
Resp	Rhinorrhoea	1 (0.1)		2 (0.7)
Skin	Rash			2 (0.7)
Gastr	Abdominal pain	4 (0.5)	2 (0.2)	
Gastr	Vomiting	4 (0.5)	3 (0.4)	

Percent basis is the number of subjects studied.
Adapted from Sponsor's table, CTD 2.7.4, Table 4-6

Table 9: Most Frequent Adverse Events (≥ 0.5%): Follow-up Phase

		Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg
No. of subjects		861 (100)	848 (100)	277 (100)
No. with any AE(s) - N (%)		55 (6.4)	32 (3.8)	18 (6.5)
SOC Abbrev.	**MedDRA Preferred Term**			
Inj&P	Overdose	6 (0.7)	3 (0.4)	7 (2.5)
Nerv	Headache	1 (0.1)	4 (0.5)	3 (1.1)
Gastr	Diarrhoea	8 (0.9)		1 (0.4)
Gastr	Abdominal pain upper			2 (0.7)
Vasc	Hypertension			2 (0.7)
Infec	Upper respiratory tract infection	6 (0.7)		1 (0.4)
Infec	Nasopharyngitis	5 (0.6)	2 (0.2)	

Percent basis is the number of subjects studied.
Overdose represents an overdose of rescue medication (rescue medication use in excess of recommended daily dose).
Adapted from Sponsor's table, CTD 2.7.4, Table 4-7

7.1.5.5 Identifying common and drug-related adverse events

The AE suspected to be related to the study drug during the treatment phase was diarrhea: lansoprazole 15 mg group, 0.6% (5/861); lansoprazole 30 mg, 0.7% (2/277) compared to placebo, 0.1% (1/848). The SOCs with the most frequently reported AEs in the treatment phase for each treatment group is the gastrointestinal disorders. See table below.

Table 10: Drug Related Adverse Events: Treatment Phase

	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg
No of subjects	861 (100)	848 (100)	277 (100)
No of subjects with any AE(s) - N (%)	15 (1.7)	11 (1.3)	14 (5.1)
SOC or Preferred term			
Gastrointestinal disorders	12 (1.4)	7 (0.8)	9 (3.2)
Abdominal pain upper	2 (0.2)		
Constipation	1 (0.1)	2 (0.2)	3 (1.1)
Diarrhoea	5 (0.6)	1 (0.1)	2 (0.7)
Flatulence	2 (0.2)	1 (0.1)	1 (0.4)
Nausea	3 (0.3)	3 (0.4)	2 (0.7)
Tongue ulceration			1 (0.4)
Vomiting	2 (0.2)		
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (0.4)
Overdose	0 (0.0)	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	0 (0.0)	2 (0.2)	0 (0.0)
Myalgia		1 (0.1)	
Pain in extremity		1 (0.1)	
Nervous system disorders	3 (0.3)	2 (0.2)	1 (0.4)
Dizziness	1 (0.1)		
Headache	3 (0.3)	2 (0.2)	1 (0.4)
Psychiatric disorders	1 (0.1)	0 (0.0)	0 (0.0)
Insomnia	1 (0.1)		
Respiratory, thoracic and mediastinal disorders	1 (0.1)		
Pharyngeal oedema	1 (0.1)		
Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.1)	4 (1.4)
Pruritus generalised			1 (0.4)
Rash			2 (0.7)
Rash generalised			1 (0.4)
Rash macular		1 (0.1)	

Percent basis is the number of subjects studied.

Sponsor's table, CTD 2.7.4, p.40

During the follow-up phase, the most frequently reported adverse events were diarrhea (0.2%, 2/861, lansoprazole 15 mg and 0.4%, 1/277, lansoprazole 30 mg groups), and constipation (0.2%; 2/848) in the placebo group. No adverse event was notably more frequent in any group.

In over 10,000 patients who have been treated worldwide with lansoprazole (Prevacid) in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment, the most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea. In short-term, placebo-controlled lansoprazole (Prevacid®) studies[5], the following adverse events were reported by the treating physician to have a possible or probable relationship to the drug in 1% or more lansoprazole-treated patients, and occurred at a greater rate in lansoprazole than placebo-treated patients (Table 11).

5 Prevacid prescription label, PDR Online accessed 9-22-08.

Table 11: Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Lansoprazole (Prevacid®) Studies

Body System/ Adverse Event	Lansoprazole (Prevacid®) (N= 2768) %	Placebo (N= 1023) %
Body as a Whole		
Abdominal Pain	2.1%	1.2%
Digestive System		
Constipation	1%	0.4%
Diarrhea	3.8%	2.3%
Nausea	1.3%	1.2%

Lansoprazole prescription label, Table 1

Headache was also seen at greater than 1% incidence but was more common on placebo.

7.1.5.6 Additional analyses and explorations

This section is not applicable.

7.1.6 Less Common Adverse Events

The Adverse Reactions section of the prescription lansoprazole (Prevacid®) label lists the following adverse experiences occurring in <1% of patients or subjects who received lansoprazole in domestic trials (number of subjects not specified) are shown below:

Body as a Whole: abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain;
Cardiovascular System: angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation;
Digestive System: abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal disorder, gastrointestinal hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, oral moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis;
Endocrine System: diabetes mellitus, goiter, hypothyroidism;
Heme and Lymphatic System: anemia, hemolysis, lymphadenopathy;
Metabolic and Nutritional Disorders: gout, dehydration, hyperglycemia/hypoglycemia, peripheral edema, weight gain/loss;
Musculoskeletal System: arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, synovitis;

Nervous System: abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased/increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo;
Respiratory System: asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor;
Skin and Appendages: acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria;
Special Senses: abnormal vision, blurred vision, conjunctivitis, deafness, dry eyes, ear disorder, eye pain, otitis media, parosmia, photophobia, retinal degeneration, taste loss, taste perversion, tinnitus, visual field defect;
Urogenital System – abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary tract infection, urinary urgency, urination impaired, vaginitis.

The prescription label also states that additional adverse experiences have been reported since lansoprazole has been marketed. The majority of these cases are foreign-sourced and a relationship to lansoprazole has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are: *Body as a Whole*: anaphylactic/anaphylactoid reactions; *Digestive System:* hepatotoxicity, pancreatitis, vomiting; *Hemic and Lymphatic System:* agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Musculoskeletal System:* myositis; *Skin and Appendages:* severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); *Special Senses:* speech disorder; *Urogenital System*: interstitial nephritis, urinary retention.

The relationship, if any, of the adverse events listed above to lansoprazole use is unknown.

Other features of prescription labeling for lansoprazole include

- No contraindications other than hypersensitivity
- No SAEs under Warnings and Precautions section of labeling

Medical Officer Comments: There are no specific warnings and precautions listed under the lansoprazole prescription label. The proposed lansoprazole OTC label warns consumers not to use the product if allergic to lansoprazole.

7.1.7 Laboratory Findings

Laboratory data were collected during the screening visit to determine eligibility for participation in each of the controlled trials. No follow-up determinations were made except at the discretion

of the investigator and no analysis of clinical laboratory data was undertaken as part of the lansoprazole OTC development program.

The prescription label (adverse event section) for lansoprazole lists the following changes in laboratory parameters and which were reported as adverse events in patients who received the drug:

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, blood potassium increased, blood urea increased, crystal urine present, eosinophilia, hemoglobin decreased, hyperlipemia, increased/decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, increased gastrin levels and positive fecal occult blood. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4/978) and 0.4% (11/2677) patients, who received placebo and lansoprazole, respectively, had enzyme elevations > 3x the upper limit of normal range at the final treatment visit. None of these patients who received lansoprazole reported jaundice at any time during the study.

7.1.8 Vital Signs

Vital signs and physical examination findings were collected during the screening visit to determine eligibility for participation in each of the controlled trials. No follow-up determinations were made except at the discretion of the investigator. No analysis of vital signs or physical examination data was undertaken as part of the lansoprazole OTC development program.

7.1.9 Electrocardiograms (ECGs)

ECG data were collected during the screening visit to determine eligibility for participation in each of the controlled trials. No follow-up determinations were made except at the discretion of the investigator. No analysis of ECG, vital sign or physical examination data was undertaken as part of the lansoprazole OTC development program.

7.1.10 Immunogenicity

Not applicable to this submission.

7.1.11 Human Carcinogenicity

There are no human carcinogenicity issues currently related to the use of lansoprazole in humans.

7.1.12 Special Safety Studies

There were no special safety studies conducted for this OTC indication.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no information to indicate that abuse or dependency occurs with lansoprazole. Prescription labeling does not describe abuse or dependency.

The sponsor provided information from the Drug Abuse Warning Network (DAWN) database from January 2003 (the inception of DAWN Live) to the end of April 2007 on cases involving lansoprazole; these were compared to the overall PPI cases. There were a total of 4,729 cases for the following five PPIs: pantoprazole 28.3%, lansoprazole 23.4%, omeprazole 22%, esomeprazole 19.6%, and rabeprazole 6.6%. The following case types had the largest proportion of cases identified for both lansoprazole and overall: adverse reaction, overmedication, suicide attempt and accidental ingestion.

In general, the distribution of drug-related diagnoses for lansoprazole did not differ markedly from the distribution observed for all the PPI cases reported. For lansoprazole cases, 12.2% (135/1,108) reported "drugs or alcohol" as a diagnostic term compared to 12.8% (603/4,729) overall; "adverse drug effects" 6% (66/1,108) compared to 6.3% (296/4,729); "overdose" 4.8% (53/1,108) compared to 4.5% (213/4,729). Among lansoprazole cases, the body system-related diagnoses reported by more than 2% of cases were: gastrointestinal 5.4% vs. 4.8% overall and cardiovascular 3.7% vs. 4% overall. The five categories of high level terms reported by more than 2% of cases for lansoprazole compared to overall cases were: allergies 5.8% vs. 4.6%, pain 5% vs. 5.1%, psychiatric conditions 3.2% vs. 3.9%, and suicide 2.8% vs. 2.3%. Both for the overall population and for lansoprazole, almost 70% of the reports involved adverse reactions. Majority of the cases were discharged home (lansoprazole 68.5% and overall 65.2%).

Overall, the range and distribution of diagnoses applied by the DAWN methodology did not show any significant differences between lansoprazole and PPIs overall. There is no information to indicate that abuse or dependency occurs with lansoprazole from the DAWN database.

Medical Officer Comments: The sponsor was asked why they did not provide information on lansoprazole from the old DAWN database (prior to 2003) since their product was approved in 1995. The sponsor explained that the availability of the restructured, on-line version of DAWN was initiated in 2003 and provides more comprehensive coverage of drug-related emergency room visits. It also offers the following advantages compared to the old version of DAWN:

- *It now uses a new sample of hospitals that now supports true national estimates.*
- *It has added metropolitan areas that the old version did not cover.*
- *It now collects data on all emergency department drug-related visits, not just those related to drug abuse; it therefore provides a more comprehensive overview of drug-related issues of medical consequence.*

- *The quality of the data collection has been improved. Different case information is collected; all emergency room charts are reviewed to ensure systematic coverage; and a formal quality assurance program has been incorporated into the data collection procedures.*

The old DAWN database was limited to visits related to drug abuse with three subcategories: suicide attempt or gesture, seeking detoxification, other drug abuse. Under these circumstances, it seems extremely unlikely that the old DAWN database would contain significant numbers of reports involving lansoprazole-related emergency department visits. Most old DAWN reports would likely involve multiple-drug suicide-related overdoses. The sponsor also contacted with Substance Abuse and Mental Health Services Administration (SAMHSA) staff on February 3, 2009 confirmed their position that the coverage of the current DAWN database, though of shorter duration than old DAWN, offers a more comprehensive and higher quality view of the emergency room visits involving lansoprazole.

The sponsor's approach to the review of the DAWN database is reasonable. The new DAWN data do not reveal any signal that lansoprazole is being abused or misused.

7.1.14 Human Reproduction and Pregnancy Data

There were no pregnancies detected during the course of the clinical trials comprising the lansoprazole OTC development program.

The prescription label states that lansoprazole is a Pregnancy Category B drug, that there are, no adequate or well-controlled studies in pregnant women, and that lansoprazole should be used during pregnancy only if clearly needed.

It is not known whether lansoprazole is excreted in human milk. Prescription labeling states that, because many drugs are excreted in human milk, because of potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue lansoprazole, taking into account the importance of lansoprazole to the mother.

Pregnancy-related reports during postmarketing:

From the sponsor's postmarketing data, there were 114 cases identified that are related to drug exposure to lansoprazole during pregnancy. More than half (55%, 63/114) of the cases either had no reported adverse effects or no fetal outcome reported. The following is a breakdown of half of the cases: 12 congenital anomalies resulting in live births, 10 non-serious cases of maternally related AEs only, 9 cases of spontaneous abortion, 8 cases of healthy infants/no abnormalities reported, 4 serious cases with fetal outcome unknown, 2 cases of still births, 2 cases of abortion (unspecified) and 1 case of each: abortion (missed), tubal pregnancy, blighted ovum and intra-uterine death.

The majority of cases had insufficient information to allow meaningful assessment of causality for lansoprazole. In cases where maternal exposure to lansoprazole during pregnancy was

followed by the occurrence of a congenital anomaly in the infant, no consistent pattern of abnormalities was suggested. It should be noted that one of every 33 babies is born with a birth defect; in the United States, about 3% of babies are born with birth defects.[6]

Spontaneous abortions occur in about 15% to 20% of all known pregnancies.[7] The spontaneous abortion reports during postmarketing did not suggest any untoward incidence that could be reasonably attributed to lansoprazole use alone.

Deaths following drug exposure during pregnancy during postmarketing:

From the sponsor's postmarketing data, there were three cases with reported outcome of fetal deaths:

- THQ2001A02326: exposure in utero to lansoprazole with fetal death at 21 weeks of pregnancy. No further information provided.
- TPG2002A00124: exposure in utero to lansoprazole with spontaneous abortion at seven weeks of pregnancy.
- THQ2003A00291: a case of a single dose of lansoprazole use in a pregnant woman; ultrasound showed a hydrocephalic fetus (dosage strength not provided). Spontaneous abortion occurred at nine weeks. No further information provided.

Medical Literature and Pregnancy

It is concluded in two publications that PPIs do not present a major teratogenic risk in humans when used at recommended doses. One study[8] published in 2005 was a multicenter prospective controlled cohort study conducted within the European Network of Teratology Information Services. The authors followed a total of 410 pregnancies exposed to omeprazole (total of 295 with 233 in the first trimester), lansoprazole (total 62, 55 in first trimester) and pantoprazole (total 53, 47 in first trimester). Results showed that the rate of major congenital anomalies did not differ between the exposed and control groups either overall or in the first trimester after exclusion of genetic, cytogenetic or infectious anomalies. Another study[9] was a meta-analysis of five published studies in 2002 which analyzed the available data on the risk for malformations following use of PPIs in the first trimester of pregnancy. The authors stated that the majority of exposures in the publications were to omeprazole; however, breakdown the distribution of exposures to PPIs was not provided. A total of 593 infants were exposed to PPIs, most often omeprazole. The summary relative risk for all major malformations was 1.18 (95% CI 0.72-1.94) among PPI-exposed infants. In addition, the meta-analytic summary incidence rate for major malformations (2.8%; 95%CI 1.8–3.8), was well within the range expected among the

6 http://www.cdc.gov/ncbddd/bd/faq1.htm#CommonBD
7 ACP Medicine Online, Ch. VIII. Ectopic Pregnancy and Spontaneous Abortion (http://online.statref.com/Document/Document.aspx?DocId=2817&FxId=48&Scroll=1&Index=1&SessionId=E4077CZPWTCNOSOR) Accessed 1-8-09.
8 Diav-Citrin O, Arnon J, Shechtman S, et.al. The safety of PPIs in pregnancy: A multicentre prospective controlled study. Alimentary Pharmacology and Therapeutics 2005; 21(3): 269-275.
9 Nikfar S, Abdollahi M, Moretti M. E., et al. Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis. Dig Dis Sci 2002, 47, 1526-9.

general population. These results are consistent with the animal data as well as with the available human case reports.

Medical Officer Comments: The information provided on pregnancy does not preclude the OTC use of lansoprazole nor warrant any changes in the current label. The risks associated with lansoprazole use in pregnant women and nursing mothers have not been formally investigated clinically; therefore, this drug should be used during pregnancy only if clearly needed. The proposed OTC label appropriately directs pregnant or nursing mothers to consult a health professional before use; this is consistent with the language of the current label of another PPI (omeprazole, a Pregnancy Category C drug) marketed for OTC use.

7.1.15 Assessment of Effect on Growth

No information was submitted regarding the effect of lansoprazole on growth. The proposed OTC lansoprazole will not be indicated in children < 18 years old.

7.1.16 Overdose Experience

According to labeling, in one reported overdose, a patient consumed 600 mg of lansoprazole with no reported adverse reaction. Lansoprazole is also not removed from the circulation by hemodialysis. In rats, oral lansoprazole doses up to 5,000 mg/kg (approximately 1,300 times the 30 mg human dose based on BSA[10]) and in mice (about 675.7 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs.[11]

Summary of Human Exposure Data from the AAPCC's Toxic Exposure Surveillance System (TESS) Database

The sponsor provided for lansoprazole exposure from 2000-2006 based on data from the American Association of Poison Control Centers' (AAPCC) Toxic Exposure Surveillance System (TESS) database, and stated that, although requested, data from the AAPCC prior to 2000 was not available for review and evaluation. The successor to TESS, now referred to as the National Poison Data System (NPDS) (implemented in September 2006) was unable to provide data on exposures before 2000.

There were 14,681 human exposures for lansoprazole with approximately 5,000 associated clinical effect (CE) terms during the reporting period. Of the 14,681 exposures, 68% (9,975) reported lansoprazole as the primary exposure; of which, 60% (8,845) reported lansoprazole as the only substance ingested. Overall, 36% of exposures occurred in children younger than 3 years, and 48% occurred in children younger than 6 years. Overall, children (≤19 years) accounted for 57% of exposures, whereas adults (≥20 yrs) accounted for 43% of exposures. Exposures resulted only in minor or moderate clinical effects when the only substance ingested was lansoprazole. These were also predominately unintentional (79.2%), mostly occurred at a

10 Body Surface Area
11 Prevacid Prescription Label 11-28-08

residence, and were managed on-site rather than in a health-care facility. Exposures were categorized as having one of the following medical outcomes: no effect, 26.5%; unrelated effect, 3%; minor clinical effect, 9%; moderate clinical effect, 5.2%; major clinical effect, 1.3%; death, 0.1% and no follow-up in 55%.

The most frequently reported clinical effects among overall lansoprazole exposures were: drowsiness/lethargy 7.13% (1,047/14,681), tachycardia 3% (445/14,681), vomiting 2.5% (370/14,681), and nausea 1.7% (246/14,681).

There were 15 (0.1%) reported deaths, all were adults ≥ 30 years old: one was unintentional, 12 were intentional (10 suspected suicides, 1 misuse, 1 unknown reason) and two were unknown reasons. Majority of deaths occurred in females (80%). All 15 deaths involved four or more reported substances, and among these drugs, lansoprazole had the least contribution to the death.

Overdose during Postmarketing
There were a total of 12 cases (involving 40 AEs) associated with an overdose of lansoprazole reported in the postmarketing database. Of these, 7 (58.3%) were non-serious cases, and 5 (41.7%) were associated with serious cases. There were no cases reported with a death outcome. Half (50%; 6/12) of the reports of overdose were for children under the age of 12 years. The most commonly reported events were accidental overdose, overdose, and medication error.

Medical Officer Comments: It appears from the TESS and Postmarketing data that lansoprazole does not represent a significant toxicologic risk. Lansoprazole has no known potential for abuse and there is no preclinical or clinical data to suggest that it has a potential for drug abuse.

7.1.17 Postmarketing Experience

Lansoprazole has been marketed with a well-characterized safety profile in the United States since its approval for prescription use in 1995 and globally for over 18 years (International Birthdate: December 31, 1990). It is currently marketed in 93 countries (as of December 2007) and an extensive safety database exists for its postmarketing experience. Six reports based on post-marketing experience with lansoprazole were provided in this submission: TAP's drug safety database, FDA's SRS/AERS databases, WHO Database, AAPCC/TESS database, Drug Abuse Warning Network (DAWN) database, and a review of the medical literature relevant to the safety of lansoprazole for OTC use.

It is to be noted that spontaneously reported case reports from the safety databases have several limitations. Among these are:

- reports are submitted voluntarily and the magnitude of underreporting is unknown
- the spontaneous reporting system yields reporting rates and not incidences
- detection rather than hypothesis testing
- clinical information may not be available in some reports

Many external factors influence whether or not an AE is reported. An accumulation of AE reports does not necessarily indicate that a particular AE was caused by the drug but rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medications. Therefore, spontaneously reported data serve only as a signal of the presence of likely cases and should be interpreted with caution.

Medical Officer Comments: This postmarketing safety review mainly addresses the single ingredient lansoprazole use in adults. Lansoprazole dosing and duration of treatment is dependent on indication. In adults the typical dose is 15 to 30 mg once or twice daily for 4 to 12 weeks depending on the indication. Although the proposed OTC use is for the 15 mg dose for 14 days, it is often difficult to determine from postmarketing information what specific dosage strength and formulation was being used by the patient. Therefore, for the purpose of this review, lansoprazole adverse events will be evaluated in general without any distinction of dosage strength or formulation.

Sponsor's Database from Postmarketing Experience

Lansoprazole was approved as a prescription product by FDA on May 10, 1995 and is marketed by TAP in the United States as Prevacid® in a variety of delayed-release formulations. The following is a review of all global post-marketing AE reports received by TAP from May 10, 1995 to September 30, 2007 for Prevacid® (lansoprazole); these cases have been forwarded to Novartis Consumer Health (NCH) per the licensing agreement. The analysis was based upon review of single ingredient lansoprazole from the TAP AE database analyzed at the System Organ Class (SOC), High Level Term (HLT) and individual Preferred Term (PT) level using MedDRA version 10.0.

As of December 2007, the estimated worldwide exposure was over —— patients to all the formulations of lansoprazole. This was estimated by dividing the total number of units shipped by the average number of units taken per patient (42 capsules or tablets per patient, based on once daily use for 6 weeks). The numbers of units are considered in terms of 30 mg capsules or orally disintegrating tablets. The 30 mg dose represents more than —— of the US consumption which in turn represents approximately —— of the consumption globally. b(4)

There were a total of 9,776 cases involving 17,768 AE terms received from May 10, 1995 to September 30, 2007. Majority of the cases (84%; 8,212) were non-serious, 13.8% (1,349) were serious and 2.2% (215) were reports of death. Table 12 presents the characteristics of all lansoprazole cases and Table 13 presents the total number of AE terms within each SOC that was reported for all cases under review (cases classified as serious may also contain non-serious events). Overall, 54.5% of the cases were from patients 18 to 74 years old; age was not provided in 22.4%. There were more reports received for females than males (61.5% vs. 34.7%); gender was unknown in 3.7% of all cases. For cases where an outcome of death was reported, there were more reports for males (51.6%) than females (46.5%), and the largest number of reports (40%) was for the age group of ≥75 years. With regard to overall case outcome: 21.8% reported recovered or recovering, 35.2% reported as not recovered or not resolved, and 40.6% reported as "unknown".

Among all 17,768 AE terms reported for lansoprazole, the most commonly reported AE (preferred) terms overall were: diarrhea, nausea, drug ineffective, abdominal pain, headache, dizziness and condition aggravated. AEs reported at a rate of ≥ 1% were identified within the following four SOCs and accounted for 37% (6,570/17,768) of all reported preferred terms.

- Gastrointestinal disorders:
  - diarrhea (1,485; 8.4%)
  - nausea (700; 3.9%)
  - abdominal pain (574; 3.2%)
  - abdominal pain upper (299; 1.7%)
  - vomiting (280; 1.6%)
  - constipation (274; 1.5%)
  - flatulence (264; 1.5%)
- General disorders and administration site conditions:
  - drug ineffective (670; 3.8%)
  - condition aggravated (376; 2.1%)
- Nervous system disorders:
  - headache (472; 2.7%)
  - dizziness (375; 2.1%)
  - dysgeusia (179; 1%)
- Skin and subcutaneous tissue disorders:
  - rash (243; 1.4%)
  - alopecia (193, 1.1%)
  - urticaria (186; 1.1%)