CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-327

SUMMARY REVIEW

Summary Basis for Regulatory Action

Date	May 11, 2009
From	Andrea Leonard-Segal, M.D., M.S. and Donna Griebel, M.D.
Subject	Division Directors' Summary Review
NDA/BLA # **Supp #**	22-327 000
Proprietary / Established (USAN) Names	Prevacid® 24 HR / Lansoprazole
Dosage Forms / Strength	Delayed-Release Capsule / 15 mg
Proposed Indication(s)	Treatment of frequent heartburn (occurring two or more days a week)
Action:	Approve with post marketing agreement if the Chemistry Inspections in Italy and Ireland are acceptable, otherwise, Complete Response.

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1. Introduction to Review

With this 505(b)(1) application, Novartis Consumer Health, Inc. seeks to switch the proton pump inhibitor (PPI) lansoprazole 15 mg to OTC status for the treatment of frequent heartburn (occurring 2 or more times per week). Lansoprazole is currently marketed by prescription under the brand name Prevacid® in 15 mg and 30 mg strengths as an oral capsule and as an injectable 30 mg formulation. The prescription indications (depending upon dose) are for the short-term treatment and maintenance of healed duodenal ulcer, short-term treatment of benign gastric ulcer, the healing and risk reduction of NSAID-associated gastric ulcer, the short-term treatment of symptomatic gastroesophageal reflux disease (GERD) and short-term treatment of erosive esophagitis, maintenance of healing of erosive esophagitis, the treatment of hypersecretory conditions including Zollinger-Ellison Syndrome and as part of triple therapy to eradicate H. pylori and to reduce the risk of duodenal ulcer recurrence. In the pediatric population (ages 1 year to 17 years), lansoprazole is approved for the short-term treatment of symptomatic GERD and erosive esophagitis. With the approval of NDA 22-327, both doses of lansoprazole would remain Rx for their current indications, but the 15 mg strength would become available OTC for the treatment of frequent heartburn indication.

Currently, the proton pump inhibitors omeprazole magnesium and omeprazole are approved OTC for the treatment of frequent heartburn in adults 18 years of age and older to be used every day for a 14-day course of treatment. The course of treatment may be repeated every 4 months if symptoms dictate the need for this. Therefore, NDA 22-327 does not provide for a new OTC indication or for a new class of OTC drug. However, if approved, lansoprazole

would become a new molecular entity available in the OTC marketplace. This memorandum will provide our assessment of the data submitted for this switch application.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Prevacid® (Takeda Abbott Pharmaceutical [TAP] Products) was initially approved in the United States as a prescription drug in 1995 for acid-related gastrointestinal disorders (NDA 20-406 and IND 30,159) and is sold as a prescription product in 93 international markets. Thus there is widespread time and extent of use of this product that enables assessment of postmarketing safety as we consider the wisdom of bringing this active ingredient OTC in the United States.

Novartis Consumer Health (NCH) has entered into an agreement with TAP granting NCH the full right of reference of their data in support of all of NCH's applications related to the OTC use of Prevacid®. NCH has informed us that the lansoprazole has been approved for OTC marketing in Sweden [ ] b(4)

3. CMC/Microbiology/Device

Yichun Sun, PhD and Moo-Jhong Rhee, PhD completed their review of the chemistry portion of the sponsor's submission on March 25, 2009 and recommended approving this NDA pending a review of the Establishment Evaluation for two international manufacturing and testing facilities, one in Italy and the other in Ireland. The drug substance, lansoprazole, used in the drug product of this NDA is the same active pharmaceutical ingredient used in several approved, marketed, prescription drug products. The drug product, Prevacid® 24 HR (lansoprazole) delayed-release capsules is a capsule filled with enteric coated granules containing 15 mg lansoprazole. The capsule shell has a pink body and teal cap with a black tamper evident band. The OTC capsules will be marketed in Lincoln, NE [ ] b(4)

The chemistry reviewers stated that the NDA provided adequate information on the raw material controls, manufacturing process, specifications and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period. The reviewers noted that the labels have the required information. As of the date of the completion of the chemistry review, the Office of Compliance had not given an overall acceptable recommendation for all of the facilities involved.

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The reviewers determined that NCH would qualify for categorical exclusion from the preparation of an environmental assessment since the concentration of lansoprazole will be less than 1 ppb.

4. Nonclinical Pharmacology/Toxicology

Refer to the review by Cindy Li, PhD and Paul Brown, PhD. The in-depth review of nonclinical safety data for this NDA can be found in NDA 20-406 (Prevacid® approved on May 10, 1995) and its subsequent supplements. The nonclinical section of NDA 22-327 contained nonclinical summaries from NDA 20-406 and supplements. It also contained 5 relevant nonclinical publications from the scientific literature (as of the end of 2007) which did not raise new safety signals. The reviewers concluded that based upon the risk-benefit analysis of the existing nonclinical information, the recently published nonclinical information, and the experience of human use, NDA 22-327 can be approved from the nonclinical perspective for adults at least 18 years of age

5. Clinical Pharmacology/Biopharmaceutics

There were no new clinical pharmacology studies conducted in support of NDA 22-327. The sponsor relied upon the data previously submitted in NDA 20-406. FDA did not request additional clinical pharmacology data from NCH and the sponsor referred to the clinical pharmacology information in the approved prescription Prevacid® package insert since the proposed OTC lansoprazole granule formulation is the same as the Prevacid® formulation currently on the market.

Lansoprazole suppresses gastric acid secretion by inhibiting the (H+K+)-ATPase enzyme system at the parietal cell secretory surface and it significantly decreases the basal acid output and significantly increases mean gastric pH. The clinical pharmacology reviewers, Insook Kim, PhD and Sue-Chih Lee, PhD determined that the clinical pharmacology is adequately supported by the clinical pharmacology information in the current prescription Prevacid® label. Particularly important aspects of the clinical pharmacology of lansoprazole that have a bearing on the labeling for this product follow.

- There is a significant food effect; food diminishes the Cmax and AUC of lansoprazole by 50 – 70%.
- Lansoprazole is 97% bound to plasma proteins and is extensively metabolized in the liver with significant biliary excretion of metabolites.
- Because, as with other PPIs, lansoprazole inhibits gastric acid secretion, it should not be co-administered with atazanavir, which is dependent upon the presence of gastric acid for absorption.
- Lansoprazole may inhibit the CYP3A4-mediated metabolism of tacrolimus resulting in increased tacrolimus concentrations in the blood, particularly in transplant patients who are not efficient CYP2C19 metabolizers.

- For geriatric patients and patients with renal insufficiency the pharmacokinetics indicate that no dosage adjustment is required. However, for patients with severe liver disease, because the mean plasma half-life is prolonged and the mean AUC of lansoprazole increased up to 500% compared with healthy subjects it was determined that a dose reduction should be considered. (In essence, this would mean from 30 mg to 15 mg.) There are no gender differences noted.
- The mean AUCs in Asian subjects are approximately twice those seen in pooled U.S. data and the Cmax values were comparable. There was high inter-individual variability noted in the studies and the prescription labeling does not recommend a dosage adjustment for Asian patients.
- Lansoprazole is metabolized through the cytochrome P450 system via the CYP3A and CYP2C19 isozymes. The metabolites have essentially no antisecretory activity. Studies in healthy subjects have demonstrated that lansoprazole does not have clinically significant interactions with other cytochrome P450 drugs such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time (PT) in patients receiving PPIs, (including lansoprazole) and warfarin concomitantly so patients treated with PPIs and warfarin may require monitoring of their INRs and PTs. There is a small (but probably not clinically significant) increase in the clearance of theophylline when co-administered with lansoprazole.
- Co-administration of lansoprazole and sucralfate resulted in a decreased bioavailability of lansoprazole but there was no evidence of an impact of antacids on the efficacy of lansoprazole.

6. Clinical Microbiology

There were no clinical microbiology data submitted with this application and none were requested by the Agency.

7. Clinical/Statistical

The sponsor submitted three multicenter, double-blind, randomized, controlled clinical studies (PRSW-GN-301, PRSW-GN-302, and PRSW-GN-305) to demonstrate the efficacy of lansoprazole 15 mg to treat frequent heartburn over 14 days in adults 18 years of age and older. Refer to the reviews by Drs Niak and Rajpal and the statistical review by Drs. Cooner and Welch for a detailed analysis of the three studies.

Efficacy

Studies 301 and 302 assessed the proportion of 24-hour days with no heartburn during 14 days of treatment as a primary endpoint. The proportion of 24-hour days with no heartburn over the first 2 days was a secondary endpoint in 301 and 302 and a tertiary endpoint in 305. Study 305 assessed the proportion of nighttimes with no heartburn during 14 days of treatment as the primary endpoint. All three studies assessed the proportion of subjects with no heartburn during Day 1 as a secondary endpoint. These endpoints were based upon the subjects' daily self-assessment regarding the occurrence of heartburn symptoms.

There were 1986 patients enrolled in these three studies and 861 of them received lansoprazole 15 mg, 277 received lansoprazole 30 mg and 848 received placebo for 14 consecutive days. There were approximately twice as many women enrolled in each treatment group as men. Approximately 70% of the enrolled population was Caucasian with the remainder of the study population Hispanic and African American. At least 95% of the subjects in each study and in each treatment group were completers. Approximately 74% of the study population in 301 and 302 had nighttime heartburn whereas 100% of the study population in 305 had nighttime heartburn.

Primary endpoints:
For studies 301 and 302 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 two treatment groups were compared by fitting an analysis of covariance 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. For each of these two studies there was a statistically significant difference in the response rates between the treatment and the placebo arm ($p < 0.0001$), supporting that lansoprazole 15 mg is efficacious.

Study 305 demonstrated that there was a statistically significant difference ($p < 0.0001$) in the response rates for nighttime heartburn between the treatment and placebo arms. Response rate for nighttime heartburn was evaluated as an important secondary endpoint in Studies 301 and 302, and found to be higher on the lansoprazole arm in both studies. The biostatistical reviewer only considered the difference to be statistically significant in Study 302. The clinical reviewers noted that these results do not mean that lansoprazole 15 mg is efficacious for the treatment of nighttime heartburn over 14 days because the definition of nighttime heartburn has not been established (the population has not been fully characterized) and there are several unrelated etiologies that contribute to nighttime heartburn. It is important to note that patients with nighttime heartburn may have a more serious underlying condition that requires professional care. Therefore, a nighttime heartburn claim may not be an appropriate OTC claim. The sponsor is not pursuing a nighttime heartburn claim at the present time, but if this were to occur in the future, this issue would need to be vetted by an Advisory Committee.

Secondary endpoints:
The statistical reviewers noted that the applicant altered the statistical plan for analysis of the secondary endpoints in Study 301 and 302 at the time of study completion. Although the changes were made before unblinding, the reviewers expressed concern that the changes were made so late that the protocols were not amended. The changes included moving the secondary endpoint of proportion of heartburn free subjects in the period Day 1 through Day 2 up from a tertiary endpoint to an important secondary endpoint. This endpoint would be analyzed in sequence after the night time heartburn secondary endpoint (which was the first to be tested in the sequence). The third important secondary endpoint,

proportion of subjects without heartburn on Day 1, was moved down in the sequence, to be tested after evaluation of the changes in the period Day 1 through Day 2.

Based on the revised hierarchy, the statistical reviewer noted that because the prespecified primary parametric analysis of the first secondary endpoint (nighttime heart burn) in the sequence was not found to be statistically significant in Study 301, the next secondary endpoints in the sequence could not be validly examined. She recommended that the results of comparisons in any subsequent secondary analyses in Study 301 could only be considered descriptive. However, the statistical reviewer noted that the Day 1 through Day 2 secondary analysis in Study 302 could be considered valid because the analysis of the first secondary endpoint in the hierarchy was statistically significant. The Day 1 analysis in Study 302 was also found to favor lansoprazole, and was statistically significant. The sequential secondary endpoint analysis of Study 302 appeared to support the sponsor's claim that lansoprazole 15 mg can be efficacious for complete relief of heartburn in some patients in the period of Day 1 through Day 2 of a 14-day trial period and in some patients on Day 1. In Study 301, the analysis of both of these two secondary endpoints were reported as statistically significant, favoring lansoprazole, however, as noted above, the biostatistical reviewer determined that these findings could only be considered descriptive. As shown in the table below, the day by day comparison of the proportion of patients reporting being heartburn free in studies 301 and 302 demonstrated that the peak treatment effect did not occur until Day 4-5.

Daily Results for Proportion of Subjects with No Heartburn over 14 days of Treatment - ITT

Study 301			
Day	Prevacid [%]	Placebo [%]	Prev-Plac [%]
1	50	33	17
2	53	46	7
3	55	43	12
4	57	44	13
5	60	42	18
6	63	45	18
7	62	43	19
8	63	45	18
9	63	48	15
10	62	47	15
11	62	46	16
12	62	54	8
13	63	53	10
14	66	51	15

Study 302			
Day	Prevacid [%]	Placebo [%]	Prev-Plac [%]
1	51	38	13
2	58	43	15
3	64	43	21
4	63	38	25
5	63	43	20
6	64	43	21
7	65	46	19
8	69.	51	18
9	67	47	20
10	69	51	18
11	69	48	21
12	66	44	22
13	70	48	22
14	70	50	20

Based on the secondary endpoint data, the applicant proposed that the product labeling should include a statement, "Although many people get complete relief of symptoms within 24 hours, it may take 1 to 4 days for full effect." The reviewers concluded that the results of the secondary endpoint analyses from these studies supported time to onset of

effect product labeling similar to Prilosec OTC's labeling, i.e., "It may take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours."

Study 305 also showed a higher proportion of 24-hour days with no heartburn over 14 days in the lansoprazole 15 mg group than in the placebo group and more subjects on lansoprazole had complete relief of heartburn on Day 1. In the analysis of the remaining designated important secondary endpoint of this study, a higher proportion of subjects in the lansoprazole 15 mg group than in the placebo group reported being free of heartburn over the period consisting of Days 1 through 2

The reviewers recommend that, from the efficacy studies standpoint, lansoprazole 15 mg could be approved for the OTC treatment of frequent heartburn in adults and we agree.

Pediatric use/PREA waivers/deferrals
A full pediatric waiver is being granted for this application based on the fact that it would not be safe to use this medication OTC in the pediatric population since the underlying causes for heartburn in children should be evaluated by a healthcare professional. This information is captured in labeling.

Safety
The data reviewed to support the OTC switch of lansoprazole 15 mg included safety data from the three clinical trials (301, 302, and 305), analysis of postmarketing AEs from the global postmarketing AE reports received by TAP (May 10, 1995 – September 30, 2007), report summarizing AEs from the SRS (1969 – October 1997) and AERS (November 1997 – June 2007), Analysis of the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) database (2000 – 2006), the Drug Abuse Warning Reports (DAWN) for lansoprazole (January 2003 – April 2007), World Health Organization (WHO) International Drug Monitoring Program (October 1993 – July 2008), medical literature (January 1988 – December 2007), Current lansoprazole prescription labeling, Proposed lansoprazole OTC labeling. Additionally, there was a 4-month safety update. The safety database was adequate.

Safety findings from submitted clinical trials
Refer to the review by Dr. Lopez and by Dr. Furlong. There were 2 reports of death from the 3 controlled clinical trials. One was a 90-year-old man in the 15 mg lansoprazole arm (Study 301) who developed angina pectoris on Day 4 during the follow-up phase and died of a cardiac arrest following a heart catheterization on Day 7. He had a history of hypertension, prostate cancer and bilateral hip replacement and was taking hydrochlorothiazide and aspirin. The second patient was a 41-year old male in the placebo group (Study 302) who had a cerebrovascular accident on Day 11 during the treatment phase. This patient had a history of hypertension, HIV, and blurred vision. Neither of these cases were thought to be related to the administration of study medication. Similarly, none of the serious adverse events that occurred during both phases of the studies appear to be study drug-related. Further, there were no signals of concern related to the reasons why people dropped out of the studies. Refer to pages 22-25 of Dr. Lopez's review.

Diarrhea was the most commonly reported adverse event in the clinical trials, followed by headache. Diarrhea was more commonly seen in the lansoprazole groups and headache was more common among those on placebo. Diarrhea may have been related to drug use. This finding is consistent with the finding that among the 10,000 patients treated worldwide with lansoprazole in Phase 2 or 3 trials at various dosages and durations of treatment, the most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea. Constipation and nausea have also been reported as being possibly or probably associated with lansoprazole use. The lansoprazole prescription labeling lists many infrequently observed adverse events across body systems with unknown relationship to drug. The labeling lists a hypersensitivity contraindication. There has been no evidence that lansoprazole causes cancer in humans.

Drug abuse/misuse

There are no data to suggest that abuse or dependency occurs with lansoprazole and the DAWN data did not reveal any signal that lansoprazole is being abused or misused. Postmarketing data on overdose, including the TESS data suggest that lansoprazole does not present a significant toxicologic overdose risk. Of the 15 reported deaths in the TESS database, all were adults at least 30 years old; one was unintentional, 12 were intentional (10 suicides, 1 misuse, and 1 unknown reason) and two were unknown reasons. Eighty percent were in females. All 15 deaths involved four or more reported substances and among these various substances, lansoprazole was felt to be the least attributable.

Pregnancy/lactation

Lansoprazole is a Pregnancy Category B drug because there are no adequate or well-controlled studies in pregnant women. Pregnant women should only use lansoprazole during pregnancy if clearly needed. It is unknown whether lansoprazole is excreted in human milk, so therefore the prescription labeling states that a decision should be made whether to discontinue nursing or to discontinue lansoprazole, taking into account the importance of taking lansoprazole to the mother. There have been postmarketing reports of drug exposure during pregnancy, but those reports are not associated with consistent patterns of fetal abnormality such that drug attribution is identifiable. Dr. Lopez reviewed data from two studies in the medical literature (in 2002 and 2005) assessing the use of PPIs during pregnancy (page 34-5 of her review) and noted that these articles do not demonstrate that PPIs present a teratogenic risk above background rate. Most exposures were with omeprazole, but there were cases of lansoprazole exposure.

It is important for the OTC label to direct pregnant or breastfeeding mothers to consult a health professional before use.

Postmarketing Data

Lansoprazole had been marketed in the United States for fourteen years and globally for nineteen. As of 2007 it is marketed in 93 countries and the estimated exposure has been to more than ——— patients, so there is an extensive postmarketing safety database. Dr. Lopez was only able to evaluate the postmarketing data for lansoprazole en masse, lacking the ability to distinguish between adverse events for the 15 mg and 30 mg strengths or for duration of use or formulation. The reports were typically in adult patients using the

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product for 4 – 12 weeks, whereas the duration of use for the OTC product will be 14 days. This suggests that the postmarketing data presented a worst case scenario because lansoprazole would be available OTC at the lower dose for the shortest approved treatment duration.

There were 215 deaths associated with 471 adverse event terms reported for lansoprazole during the postmarketing period from May, 1995 to September 30, 2007; 37.2% of these cases were from Japan and 4% were from Columbia. Seventy-one percent of the cases were categorized as Category 2 (confounding factors are documented that may possibly have contributed to death), 24% were Category 3 (poorly documented case where a relationship between lansoprazole use and death could not be determined), and 5% (10 cases) were Category 1 (no documentation of confounding factors documented or lansoprazole could not be reasonable excluded as a factor possibly contributing to death). Dr. Lopez analyzed the 10 cases in her review and determined that they do not appear to show any trend or pattern of reporting and that a clear temporal relationship between the use of lansoprazole and death cannot be determined in most of the cases due to confounding underlying medical conditions and drugs. We agree with her analysis.

There were 1,349 serious cases reported during the same time frame. The most commonly reported preferred terms associated with the serious cases were diarrhea, pyrexia, drug interaction, condition aggravated, abdominal pain, anaphylactic reaction, dizziness, nausea, vomiting, thrombocytopenia, and rash. These are known adverse events that are included in the current prescription labeling for lansoprazole with the exception of "condition aggravated." This term was generally used to reflect concomitant disease aggravation.

Hip fractures in the elderly have been reported in the medical literature associated with the use of PPIs. The agency is currently evaluating this association for the PPI drug class. Three cases of hip fracture were noted in the review of the postmarketing database for lansoprazole. Should the agency determine in the future that class labeling is warranted for prescription PPIs regarding fracture risk, a warning will be added to all OTC PPI labels as well. However, it is important to note that because OTC PPIs are only labeled for 14 days of use, no more than 3 times per year, it is possible that OTC products may present less of a risk than the prescription products with their longer duration of therapy.

Dr. Lopez concludes that there are no new or unexpected safety signals in the postmarketing database for lansoprazole and that the majority of adverse events reported are not serious, mild, and self-limiting. The most frequent events were diarrhea, nausea, abdominal pain, and drug ineffective.

FDA SRS and AERS Databases
It is not clear how many of the reports in this database were duplicates. There were 394 deaths reported, but no single organ system or disease consistently associated with these reports and there were no new adverse events reported at a significant frequency. Reported adverse event terms were sepsis, pneumonia, pyrexia, hepatic failure, condition

aggravated, thrombocytopenia, multi-organ failure, disseminated intravascular coagulation, gastrointestinal hemorrhage, and renal failure. For the serious adverse events, again, there were no new signals and no consistent pattern of reports and it is difficult to make attribution to lansoprazole versus the underlying medical illness for which the patients were treated. The databases did not reveal any new safety concerns associated with lansoprazole.

WHO Data
The sponsor provided adverse event data from the WHO from 1993 to July, 2008. The types of adverse events in this database were consistent with those seen in the others and with the current prescription labeling for lansoprazole. There were no new or unexpected signals.

Safety Update
The sponsor submitted a 4-month safety update providing summaries of postmarketing reports from October 2007 to July, 2008, literature review from January 2008 to July 2008, WHO through August 2008, and the FDA SRS and AERS databases through June 2008. Dr. Lopez reviewed this safety update submission and found the reporting to be consistent with previous reporting. No new signals were noted.

Drs. Lopez and Furlong conclude that lansoprazole is has well-characterized safety profile and is a safe drug. They state that there should be no new unexpected safety signals if the 15 mg dose is marketed OTC for a two-week treatment course. They recommend that from the clinical safety standpoint, the application should be approved.

Consumer Studies:
It is important to point out that lansoprazole does not represent a first in class prescription to nonprescription switch and the labeling is virtually identical to that for Prilosec OTC. For these reasons, there was no need to perform consumer studies for this NDA.

8. Advisory Committee Meeting

There was no Advisory Committee Meeting convened for this application. This is not a first in class switch and the labeling for this product does not present new indications, warnings, or directions for use for the OTC consumer. The application did not present new or controversial efficacy, safety, or consumer behavior issues that would have triggered the need for a meeting.

9. Other Regulatory Issues

This is a 505(b)(1) application and there are no patent issues. The sponsor did conduct 3 clinical trials that were essential to the approvability of this product.

10. Financial Disclosure

NCH submitted FDA form 3454 certifying that they had not entered into any financial arrangement with the listed clinical investigators such that the value of the compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a). No financial disclosures cast doubt on the findings of these studies.

11. Labeling

The labeling for this product has been reviewed by the medical reviewers in the Division of Nonprescription Clinical Evaluation and the Division of Gastrointestinal Products and by the labeling reviewers in the Division of Nonprescription Regulation Development. The trade name has been approved by the Division of Medication Error Prevention and Analysis. There have been many communications between the agency and the sponsor over the label and the package insert and the sponsor has complied with all agency requests. The labeling is acceptable.

12. DSI Audits

Four sites were inspected for the three protocols (PRSW-GN-301, PRSW-GN-302, and PRSW-GN-305) and it was the conclusion of Drs. Leibenhaut and Lewin that the studies appear to have been conducted adequately and the data generated may be used in support of the respective indication.

13.Conclusions and Recommendations

Prevacid® 24 HR is safe and effective for the OTC treatment of frequent heartburn for 14 days in adults 18 years of age and older. The treatment may be used up to 3 times per year with treatments 4 months apart. This product should be approved, provided that the two incomplete international CMC inspections (in Italy and Ireland) are acceptable.

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/s/

Andrea Segal
5/11/2009 10:25:04 AM
MEDICAL OFFICER
This is a joint review by the Director of the Division of Nonprescription Clinical Evaluation and the Director of the Division of Gastroenterology Products.

Donna Griebel
5/11/2009 10:31:01 AM
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