CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-987

MEDICAL REVIEW(S)

W9CSM

SEP 17 [illegible]

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-987
Sponsor:	Wyeth-Ayerst Research (W-AR) Philadelphia, PA
Date Submitted:	August 18, 1999
Drug:	PROTONIX® (pantoprazole sodium)
Pharmacological Category:	Gastric Acid Antisecretory, Anti-GERD, Anti-ulcer. Inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell
Approved Indication:	Short-term treatment of erosive esophagitis in patients with gastroesophageal reflux disease (GERD)
Formulation/Mode of Administration:	40 mg Delayed-Release Tablets for oral administration
Material Reviewed:	W-AR submission dated August 17, 1999 in response to the Agency's June 30, 1999 approvable letter which included recommended changes to the draft labeling
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D. Medical Team Leader

I. BACKGROUND

PROTONIX® (pantoprazole sodium), NDA 20-987, is a proton pump inhibitor with established efficacy in the healing of erosive esophagitis associated with GERD. In the approvable letter dated June 30, 1999, the sponsor was asked to address labeling, and other issues, including Phase IV commitments.

It was explained that the overall assessment of safety in humans was sufficient to support the indication for use up to 8 weeks, with consideration of an additional 8 weeks of therapy in patients who had not initially responded. A precautionary statement regarding long-term use of the drug and the findings of animal carcinogenicity and genotoxicity will have to be included. Consequently, a draft labeling was prepared by the Division taking into consideration these

recommendations while using as overall models, the labeling for PRILOSEC® (omeprazole) and PREVACID® (lansoprazole), the two marketed PPIs.

In their July 30, 1999 response to our approvable letter, the sponsor provides a revised labeling and complete responses to the Agency Comments. This review addresses **exclusively the clinical matters** related to the labeling proposed by the sponsor in their response to our Approvable Letter. The review is structured as follows.

The two versions (proposed by the Agency vs proposed by the sponsor) of each item where modifications are proposed are displayed side-by-side; the paragraph number is used to identify the PI area being considered. The rationale provided by W-AR for the change to our Draft Labeling is then given. This is followed by a reviewer's **Comment (RFRA=Recommendations for Regulatory Action)**. The RFRA includes a recommendation to either accept or reject the change proposed by W-AR and a justification in support of the reviewer's recommendation. Changes throughout the labeling to provide the product description as delayed-release tablet are usually not commented upon. Accordingly, the present review does not contain the customary (usually separate) section on Recommendations for Regulatory Action because these are given throughout.

a. Paragraph 27

FDA Comments/Revisions	W-AR Comments/Revisions
[redacted]	[redacted]

W-AR's rationale

Changes to this paragraph were made for clarity.

COMMENT (RFRA)

Acceptable changes indeed made for clarity.

b. Paragraph 28 and 29 (also 36 and 37)

Paragraph 28 consists of a Table describing the percentage of healing rates observed in a US endoscopically diagnosed EE study comparing grading doses of PROTONIX to

placebo. In paragraph #29, the sponsor was asked to revise this Table to include data from the ITT analysis rather than the per protocol analysis.

The sponsor does not accept this change.

W-AR Rationale

The sponsor provides the following 6 reasons to justify displaying results based on the VFE (verified for efficacy; per protocol)[1] population rather than ITT population: (1) the two ITT approaches[2] were chosen to represent the extremes of response and are considered upper and lower bounds on the true response in this population. Neither of the ITT approaches is likely to provide a more accurate estimate of the true response rate than the VFE population; (2) if the ITT results were shown, an explanation of how they were obtained should be included. This would add an unwanted level of complexity to the product label; (3) the VFE results for study No. 300 include the large majority of the patients randomized to treatment depending on the dose and the visit, from 88% to 92% of the pantoprazole patients and 83% to 94% of the placebo patients. For study No. 301, the VFE percentages are from 86% to 93% for pantoprazole and 85 to 88% for nizatidine; (4) the statistical conclusions about the relative effectiveness of the four treatments in study No. 300 are identical regardless of the population on which the analyses are based. Similarly, the statistical conclusions about the relative effectiveness of the three treatments in study No. 301 are identical regardless of the population on which the analyses are based; (5) there was no identification of a primary analysis population in the protocol or at the pre-NDA meeting with FDA. Presenting the VFE data would not represent a change from any previous plan or agreement and (6) per protocol analyses (equivalent to our VFE analyses) have been presented in the product label for other proton-pump inhibitors (please see Prilosec labeling). Displaying the VFE results for pantoprazole would make it consistent with these other labels.

Comments (RFRA)

It is recommended to accept the sponsor's explanations to display data from per protocol rather than ITT analyses. The two ITT approaches were described in detail in the MOR of NDA ——— their description would complicate the labeling unnecessarily. This mode of presentation (per protocol) is in keeping with the presentation of percent healing rates with PRILOSEC (omeprazole) in GERD trials (page 585 of 1999 PDR). The MTL is of the opinion that the efficacy of pantoprazole against either placebo (in one trial) or nizatidine (in the other) is very robust (as shown by very large therapeutic gains). Therefore, in this instance, it makes little, if any, difference whether ITT or VFE data are

[1] The VFE analyses (per protocol analyses) excluded those patients who had no post-baseline endoscopy plus some additional patients who violated the protocol (e.g., missed test medication, unacceptable concomitant medication).

[ ]

displayed. The message of clear-cut efficacy of the drug is given equally well by one or the other mode of data presentation.

c. **Paragraphs 31, 32, 33 and 35 (Clinical Studies)**

FDA Comments/Revisions	W-AR Comments/Revisions

W-AR Rationale

The sponsor states that during the end of Phase II meeting held in October 1996, the Division Director specifically requested that the proposed primary studies to support efficacy and safety (study Nos. 300 and 301) include at least 30% of patients with severe erosive esophagitis, grades 3 and 4, and that additional subgroup analyses be performed for these patients. In accordance with the Agency's directive, W-AR included more than the specified percentage of grades 3 and 4 patients and performed the requested analyses. Thus, according to the sponsor, it seems appropriate to include the results of these FDA-requested analyses in this section.

In paragraph 32, per FDA request, W-AR has removed

In paragraph 35, more specific information regarding the dosages used is provided for clarity.

Comment (RFRA)

It is recommended not to include in the labeling data on the **"most severe grades of esophagitis"**, an issue that was clearly addressed in the MOR of NDA 20-987 of April 19, 1999.

The grading system used in both critical clinical trials (300-US and 301-US) was the Hetzel-Dent scale. With this scale, erosive disease is graded as follows:

Grade #	Severity of Esophagitis
1	No esophagitis
2	Mild
3	Moderage
4	Severe

In both trials the percentage of patients who at baseline had Grade 4 esophagitis was rather **low**:

Esophagitis Grade 4	Overall Percentage of Patients in Trial	Source (MOR of April 19, 1999)
Study 300	7.8% (average of three dose levels of the drug, 10, 20 and 40 mg once-a-day and placebo)	Table 8, page 34
Study 301	9.1% (average of two dose levels of the drug, 20 and 40 mg and nizatidine 150 mg QD)	Table 24, page 65

In Section 12. of the MOR of study 300-US, "Reviewer's Additional Comments", third paragraph of page 55, the reviewer states:

> ".....Since there were not too many patients with grade 4 (severe) esophagitis included in the ≥3 pooled category, the reviewer concludes that PANTO 40 mg **provided the greatest healing rates for both mild and moderate esophagitis**. Experience with esophagitis of the severe type is too limited and no firm conclusions can be drawn at this time"

Similarly, in Section 12. of the MOR of Study 301-US, "Reviewer's Additional Comments", first paragraph of page 85, the reviewer states:

> "....However, as in Study –300-US, since there were not too many patients with grade 4 at baseline included in the ≥3 pooled category, the reviewer concludes that PANTO 40 mg provided the greatest healing rates for both mild and moderate esophagitis.

Experience with esophagitis of the severe (Grade 4) type is too limited and no firm conclusions can be drawn at this point in time."

In summary, although clear-cut efficacy was shown in both trials, approximately 90% of the study population consisted of patients who had **mild to moderate** esophagitis at baseline. Only <9% of the patients had esophagitis Grade 4 (severe) at baseline. It is therefore inappropriate to pool the severe with the moderate category and term the pooled data as the **"most severe grades of esophagitis"**. Data from both trials showed that, in both studies, the experience with esophagitis of the severe (Grade 4) category was too limited and no firm conclusions (regarding healing of this most severe grade of esophagitis) could be drawn from these studies.

d. Paragraph 40 (INDICATIONS AND USAGE)

FDA Comments/Revisions	W-AR Comments/Revisions
[redacted]	

W-AR Rationale

In the sponsor's version of the labeling, the statements, [redacted] " have been revised. The sponsor states that this revision is being proposed to "avoid confusion." According to the sponsor, the latter statement could be misleading since two courses of 8 weeks are allowed. In lieu of the above, the sponsor proposes to insert the statement, "The safety and efficacy of PROTONIX® for maintenance therapy (e.g., beyond 16 weeks) have not been established." [redacted] The sponsor further explains that this change will mitigate potential discrepancies with international core product labeling, while providing the FDA-requested information on length of appropriate use in patients with EE.

Comment (RFRA)

The reviewer does not agree with the sponsor's proposal, although admittedly, the phrase "an additional 8 week course of PROTONIX may be considered" appears to be incongruent with the phrase [redacted]. The FDA intent is to convey at least four messages with respect to the indication for which PROTONIX has been approved and the usage of the drug when prescribed for that indication: 1) short-term treatment (defined as up to 8 weeks); 2) the possibility of considering an additional 8-week course for those patients who have not healed after the initial 8 weeks of treatment (the net result of this is an extension of the short-term definition from 8 to up to 16 weeks); 3) not to use PROTONIX as maintenance therapy (meaning continuous daily administration beyond 16 weeks); and 4) not to administer repeated courses of the drug (whatever the length of treatment, 4, 8 or 16 weeks over and above the initial up to 16 weeks). In reality, the labeling is saying that, if the patient needs antisecretory/PPI medication for longer than 16 weeks, **in fact maintenance therapy**, he/she should not be prescribed PROTONIX. In other words, erosive EE healing should not be maintained with the drug administered in an **intermittent fashion**.

The sponsor's proposal is not strong enough with regard to FDA decree that the drug should not be used as maintenance therapy; the sponsor's proposed wording is almost an invitation to use the drug for maintenance therapy.

The reviewer proposes the following wording: [redacted]

e. Paragraph 41 (CONTRAINDICATIONS)

Comment (RFRA)

This change, to provide the product description as delayed-release tablets, is acceptable.

f. Paragraphs 42 and 43 (PRECAUTIONS)

APPEARS THIS WAY
ON ORIGINAL

FDA Comments/Revisions	W-AR Comments/Revisions
42 PRECAUTIONS	PRECAUTIONS

W-AR Rationale

In the W-AR version of the labeling, the sentence, [redacted]" was modified to appear at the end of the section in a separate paragraph, along with the statement that the relevance of animal findings to clinical use is not known. The sponsor states that since the CAC (at the May 27th meeting) validated by their 10 to 7 vote that the genotoxic potential of pantoprazole is comparable to that of omeprazole and lansoprazole, inclusion of genotoxicity information in this section is considered unnecessary. W-AR further explains that the statements, [redacted] have been revised to avoid confusion. The latter statement could be misleading since two courses of 8 weeks are allowed. In lieu of the above, the statement, "The safety and efficacy of PROTONIX® for maintenance therapy (e.g., beyond 16 weeks) have not been established," has been inserted to "reflect the current understanding and status of the product within the US." The sponsor is of the opinion that this change will mitigate potential discrepancies with international core product labeling, while providing the FDA-requested information on length of appropriate use in patients with EE.

Comments (RFRA)

The reviewer does not agree with the sponsor's proposed wording because it does not express the need to be **cautious to prevent harm**. W-AR's proposed sentence "the safety and efficacy of PROTONIX for maintenance therapy (e.g. beyond 16 weeks) have not been established" seems out of place. Although we all agree that the relevance of animal findings to clinical use is not known, the sponsor's sentence [redacted] is considerably downgrading the importance of the pre-clinical findings and seems to be expressed in an almost perfunctory fashion. Additional explanations by the sponsor are a repeat of W-AR's rationale for the above-addressed proposed changes

to paragraph 40 (INDICATIONS AND USAGE). This reviewer does agree with the sponsor that, when all available information is taken into consideration, the genotoxic potential of pantoprazole is similar to that of the other (already approved) PPIs. But, incorporating this information in the labeling is important to present a more complete toxicological characterization of the drug. This message is balanced by incorporating the statement "while risk to humans is unknown" in this section.

In a fashion analogous to that proposed when addressing changes to paragraph 40 (INDICATIONS AND USAGE) above, the reviewer proposes the following wording:

[ ]

f. Paragraphs 44 through 48 (Information for Patients

FDA Comments/Revisions	W-AR Comments/Revisions

W-AR Rationale

In addition to the change made to provide the product description as delayed-release tablets, the sponsor proposes

a) To delete the phrase ——— because there was no restriction in Protocols 300 and 301 regarding the type of fluid to be imbibed with PROTONIX.

b) In the absorption subsection, it is said that the presence of food should have no clinical significance on the onset of response with pantoprazole treatment. It is concluded that PROTONIX may be taken without regard to the timing of meals.

c) Paragraph 48, on the potential interferance of drug absorption with pantoprazole has been moved to follow the drug interaction paragraph since it is more closely related to that discussion.

[

]

[

]

Comment (RFRA)

The sponsor's justification for the requested changes a) through e) above, in paragraph 44 through 48, appear reasonable to this reviewer. Acceptance of these changes which should also be evaluated by Biopharm, is recommended.

g. **Paragraphs 60 through 80 (ADVERSE REACTIONS)**

FDA Comments/Revisions	W-AR Comments/Revisions
[	

2 PAGE(S) REDACTED

Draft

Labeling

W-AR Rationale

The sponsor has updated this section to include information submitted in the Safety Update in February 1999.

a) There are now >11,100 patients (instead of 8900) that have been treated with pantoprazole in clinical trials.

b) Paragraph 62

The sponsor explains that the information presented in the original table of Drug-Related Adverse Events in Short-Term Domestic Trials was generated from two controlled and blinded studies which are referenced in the preceding paragraph. The table previously included data from the combined pantoprazole populations from study Nos. 300 and 301 plus separate data for the control groups of nizatidine from study No. 301 and placebo from study No. 300. According to the sponsor, the change which the Division recommends, i.e. deleting the nizatidine column would create an impression that the data in the table represent a single study and that only one control group was used in safety assessment.

W-AR further explains that the table in their revised labeling presents in an "unequivocal manner" the safety data obtained from two studies that are clearly identified in the table under the headings of studies Nos. 300 and 301. The criteria to construct the table remain the same as for the original table, i.e. data presented are considered to be possibly, probably or definitely related to drug that occurred with the frequency of 1% or more and the frequency of occurrence was equal or more than that in the corresponding control groups. It is noted that the number of events listed in the revised table is greater than that in the original table. This relates to the fact that the denominator has changed when partoprazole data are presented separately for the two studies. Thus two adverse events, **insomnia** and **hyperglycemia** reached a frequency of 1% and are now included in the table. The sponsor concludes that this revised table provides a more complete and

understandable presentation of the safety data from the Wyeth conducted studies which provided the primary evidence of safety and efficacy.

c) The sponsor makes no specific reference to changes to paragraphs 63, 64 65, 68, 74, 75 and 78.

d) Paragraphs 66, 67, 69 through 73, 76, 77 and 80

Changes accepted as per FDA recommendations; no further revisions.

e) Paragraph 79 **(Postmarketing Reports)**

In reference to this paragraph, the sponsor explains that the FDA text described the current spontaneous reports that exist (i.e., international in nature). It was however, deemed more appropriate to reflect spontaneous reports without regard to country of origin, since, post-US approval, spontaneous reports may also be received from the US and a separate paragraph describing spontaneous reports for each country would burden the PI. In addition, the sponsor explains that it is not necessary to describe spontaneous reports as serious and unexpected and possibly related in the labeling, since, by definition for their inclusion the labeling they meet this classification [21 CFR 201.57 (g)]. In addition, the change to this sentence is consistent with a Wyeth internal draft labeling guideline which was not in effect at the time of the NDA submission for PROTONIX. The goal of this new internal guideline is to use clear, simple language to ensure that health professionals are able to understand the information provided.

Further changes in this paragraph include additional spontaneous reports received since the draft labeling was first submitted. The eponym "Lyell's syndrome" was replaced by the terms **toxic epidermal necrolysis** and **TEN**, which are the synonymous terms for this condition commonly used in the US. Although it was the AE term used in the spontaneous reports from Byk Gulden, "Lyell's syndrome" is not a readily recognized condition to most American physicians. The paragraph was also re-organized alphabetically; however, the related serious skin reactions (erythema multiforme...) were kept together.

Comment (RFRA)

With the exception of the nizatidine ARs issue (see below), all changes to the ADVERSE REACTIONS section of the PI, requested by the sponsor, are justifiable and therefore acceptable. Information submitted in the February 1999 SU is now included and updated;. >11,100 patients instead of the previous 8900 have been treated with

pantoprazole in clinical trials. The addition of the phrase in the individual studies to paragraph 61, adds important clarification.

Although the sponsor makes no reference to specific changes to paragraphs 63, 64, 65, 68, 74 and 78, all of these revisions are acceptable. The addition of terms is a consequence of the updating of the AE profile of the drug; duplications are corrected and important clarifications (for example, in paragraph 65 "based on pooled results from either" ...) have been added. In reality, no term has been deleted. Terms such as insomnia and hyperglycemia, which reached a frequency of 1% are now included in the AE Table. In reference to this AE Table, the reviewer reiterates his recommendation not to include

The reviewer agrees with the sponsor's explanations regarding the revisions, reorganizations and further changes in reference to paragraph 79 (Postmarketing Reports) (see section e above).

h. Paragraph 81 (Laboratory Values)

No changes requested.

i. Paragraph 83 (Overdosage)

FDA Comments/Revisions	W-AR Comments/Revisions

W-AR Rationale

The sponsor explains that the only revision to FDA's paragraph is the mg/kg value for mice. [In mice, the lowest oral dose of pantoprazole causing lethality was 709 mg/kg (expressed as the free acid, as are the other values in this paragraph) rather than

Comment (RFRA)

This revision, based on data presented in the study report seems acceptable but, for completeness it should also be considered by Pharm Tox.

j. Paragraphs 84 through 88 (DOSAGE AND ADMINISTRATION)

W-AR Rationale

The sponsor's rationale for these revisions was given above (see Hepatic Impairment, Drug Interaction and Absorption subsections).

Comment (RFRA)

These revisions are acceptable. Specifically the statements in paragraph 86 through 88 have been altered to be consistent with the changes in the following subjections: Hepatic Impairment, ——————— and Absorption (food effect). In addition, the phrase ——— has been deleted and this is justified because there was no restriction in protocol 300 and 301 regarding the type of fluid to be imbibed with PROTONIX. The sponsor's proposed revision should also be considered by Biopharm.

September 17, 1999

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-987
HFD-180
HFD-180/LTalarico 9-23-99
HFD-180/SAurecchia 9/23/99
HFD-180/HGallo-Torres
HFD-181/MWalsh
HFD-180/JChoudary
HFD-180/LZhou
HFD- 870/David Lee
r/d 9/14/99 jgw
f/t 9/17/99 jgw

APPEARS THIS WAY
ON ORIGINAL

Cat/Wiley

DIVISION OF GASTROINTESTINAL AND COAGULATIONS DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-987 APR 19 1999
Sponsor:	Wyeth-Ayerst Labs. Inc. Philadelphia, PA
Drug:	PROTONIX™ (Pantoprazole sodium)
Route of Formulation/Administration:	Enteric-Coated Tablets for Oral Administration
Pharmacological Category:	Gastric Acid Antisecretory, Anti-GERD, Anti-Ulcer, Inhibitor of the H^+-K^+/ATPase
Proposed Indication:	Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD)
Material Submitted/Reviewed:	Volumes 1.162 through 1.315 and 1.1 and 1.2 of the Clinical Review Section
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

EXECUTIVE SUMMARY

Wyeth-Ayerst Labs., Inc., has submitted NDA 20-987 and requested approval of PROTONIX™, an enteric-coated tablet formulation of the proton pump inhibitor pantoprazole 40 mg once-a-day to be used for up to 8 weeks for healing of esophagitis and resolution of associated symptoms associated with GERD. From the pharmacodynamic perspective, this dose of pantoprazole (40 mg) has been associated with significantly higher acid inhibition effects than the 20 mg dose of the drug. In support of this request, the sponsor has submitted data from two well-designed and apparently well-executed clinical trials. One of these studies addressed pantoprazole dose-ranging (10, 20 or 40 mg/day) comparable to placebo, the other consisted of a comparison of pantoprazole 20 or 40 mg per day to nizatidine at the recommended dose of 150 mg twice-a-day. Both trials included endoscopic evaluations of esophageal lesions healing at 4 and 8 weeks of treatment. For both healing of lesions and the relief of symptoms associated with GERD at 4 and 8 weeks of treatment, convincing superiority of pantoprazole 40 mg/day over placebo and two lower doses of the drug (10 and 20 mg/day) was shown in one trial, while the other showed great superiority of the drug (40 as well as 20 mg/day) over the approved regimen of nizatidine. Safety was similar to that of the control groups in these two studies.

Approval of pantoprazole 40 mg once-a-day —— 8 weeks) for the healing of erosive esophagitis and the relief of symptoms associated with GERD is recommended.

Superiority of pantoprazole over nizatidine for healing of erosive esophagitis and relief of symptoms associated with GERD may be claimed.

TABLE OF CONTENTS

I. BACKGROUND

In this section, a brief description of the clinical condition to be treated is given. This is followed by a short summary of the pharmacological characterization of pantoprazole [PANTO].

A. Gastro-esophageal-reflux Disease (GERD)

The term GERD encompasses a spectrum of clinical manifestations due to reflux of stomach and duodenal contents into the esophagus. Two main forms of this condition are recognized: erosive esophagitis where symptoms of reflux are accompanied by esophageal damage (i.e. erosions, ulcer) and symptomatic GERD, where symptoms of reflux (mainly diurnal and nocturnal heartburn) are not associated with endoscopically proven esophageal damage. The differentiation between these two forms of GERD is clinically important because erosive esophagitis (but not symptomatic GERD) may give rise to serious complications such as esophageal narrowing and stricture, esophageal ulcer and hemorrhage, pulmonary aspiration, or Barrett's esophagus (a premalignant condition). Also, the amount of gastric acid antisecretories to treat erosive disease is usually higher (and in the case of H_2-blockers must be administered more often) than that needed to treat symptomatic GERD.

Heartburn, ranging in degree from mild to severe, is the most common symptom of GERD (whether erosive or not) and is often associated with regurgitation of acidic material. Dysphagia, odinophagia, bleeding from esophageal lesions and stricture formation also occur.

One sensitive test for the presence of acid reflux consists of monitoring esophageal pH with a luminal pH probe for periods of up to 24h. It is important to note, however, that although this test may show that reflux indeed exists, it does not necessarily follow that reflux is responsible for the patient's symptoms. In addition, symptoms due to acid reflux do not always correlate with the extent of damage to the esophageal mucosa. Endoscopy with suction biopsy is the most sensitive test for reflux-induced mucosal damage, but in clinical trials, biopsy is usually omitted.

In erosive esophagitis, the indication sought in the present NDA, the goal of treatment is to decrease the volume and increase the pH of secretions refluxed into the esophagus. This is expected to facilitate the healing of the damage of the esophageal mucosa (primary endpoint of efficacy) and relieve the primary symptom of heartburn (secondary endpoint of efficacy). Some practitioners prescribe eradication regimens when infection with *Helicobacter Pylori* co-exists with erosive esophagitis. However, the pathogenic role of *H. Pylori* infection in GERD remains controversial.

Medications available for the treatment of erosive esophagitis include H_2-receptor antagonists (cimetidine, ranitidine, famotidine and nizatidine), which are usually administered in divided doses and proton pump inhibitors [PPIs] (omeprazole, lansoprazole) which are effective when administered once-a-day. It has recently been

hypothesized that [redacted], but this important clinical observation needs to be adequately confirmed.

Because, in the present NDA, one of the critical trials consists of a comparison of PANTO to an H_2-receptor antagonist [——— , nizatidine=NIZ], the EE healing rates with those H_2-blocker are reproduced in Table 1. The reviewer recognizes that these are historical data. But, as it will be seen later, the performance of NIZ in these PDR-described trials is closely replicated in the sponsor's critical trial.

TABLE 1

Healing Response of EE to NIZ[a] 150 mg b.i.d.[b]

	Healing Rate at Week		
	3	6	12
	Study #1		
NIZ (n=88)	16%	32%	
PL (n=98)	7%	16%	
Therapeutic Gain[c]	9% [p<0.05]	16% [p<0.05]	
	Study #2		
NIZ (n=99)		21%	29%
PL (n=94)		11%	13%
Therapeutic Gain[d]		10% [p<0.05]	16% [p<0.01]

a) [redacted]

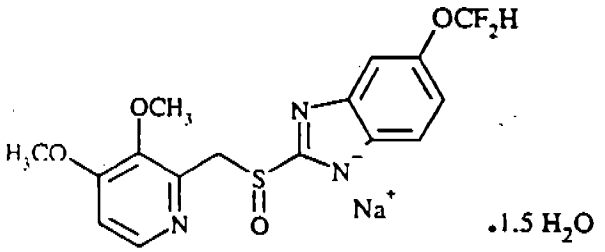
b) This is the recommended oral dosage in adults for the treatment of erosions, ulcerations, and associated heartburn.
c,d) [NIZ > PL]

B. Pantoprazole (PANTO)

1. Introduction

PANTO is a substituted benzimidazole that suppresses gastric acid secretion by specific inhibition of the action of the enzyme H^+/K^+-ATPase, the proton pump which exchanges luminal potassium for cellular hydrogen ions [E.E. Fellenires et al. Nature 290:159-161 (1981)]. This enzyme, involved with the parietal cell is the final common pathway of gastric acid secretion. Inhibition of this proton pump by PANTO (and approved PPIs ome- and lansoprazole) abolishes response to all types of acid stimulation, by all gastric messengers (e.g. histamine, gastrin and acetylcholine). When stimulated to secrete acid, the gastric parietal cell undergoes morphologic alteration with formation of secretory canaliculi. The chemical structure of PPIs is such that, in an acidic environment,

rearranges and cyclizes. This molecular rearrangement of PANTO (and other PPIs) is necessary for biological activity.



$C_{16}H_{14}F_2N_3NaO_4S$
x 1.5 H_2O

Mw = 432.4

Sodium 5-(difluoromethoxy)-2-[[(3, 4-dimethoxy-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole sesquihydrate

Following systemic absorption, PANTO (ca. pKa of 40) is protonated in the low pH environment of the parietal cell or in the acid-transporting, gastric-derived vesicles of those cells. The concentrated protonated species forms a **tetracyclic sulfenamide**, which then becomes covalently bound to cysteine-813 residues (thiol group) of the H^+/K^+-ATPase. A stable disulfide is formed that inhibits the activity of the proton pump. Since the reaction is covalent, the inhibition is long-lasting.[1]

2. Brief Summary on Nonclinical Pharmacology

Since a Pharmacology/Toxicology review is not yet available, the following information was summarized from the sponsor's Application Summary (vol. 1.002).

In several models in rats and dogs, PANTO was shown to be as potent and long-lasting inhibitor of gastric acid secretion regardless of the mechanism of acid stimulation (secretagogues actions at different receptors of the parietal cell, neurons, or paracrine cells) and regardless of the route of administration (PO dosages were similar in effect to i.v. administration; this will be further discussed on the basis of human data), indicating that PANTO has good oral bioavailability. Prevention of ulcer formation and acceleration of ulcer healing has also been demonstrated in animals. PANTO exhibited in vitro **bactericidal activity** against H. pylori. This activity required the same acid-induced transformation of PANTO as that needed for its antisecretory activity. In addition to being bactericidal in vitro, PANTO was found to **potentiate the antibacterial activity** of amoxicillin, clarithromycin and tetracycline in vivo in mice infected with *H. pylori*, although the PO dosage used in these tests was high (88.7 mg/Kg three times per day for 4 days).

[1] By comparison, agents that act by blocking, specifically, gastric stimulatory factors (such as NIZ and other H_2 receptor antagonists, anticholinergics, anti-gastrins) generally produce a less profound and less prolonged inhibition of gastric acid secretion.

Evaluations of PANTO were carried out in a variety of animal pharmacology tests, designed to identify side effects due to the drug itself or due to interactions with other pharmacological agents. In most of these studies, the dosages tested were much higher than the intended therapeutic dosage (orally administered 40 mg per day). From these studies, the sponsor concluded that PANTO has no serious side effect liability.

3. Brief Summary on Toxicology and Drug Metabolism

In the Application Summary (vol. 1.002), the sponsor provided an overview of PANTO-related findings in major toxicity and drug metabolism studies. The toxicity of PANTO was evaluated in acute PO and I.V. studies in mice, rats, and dogs, in repeated-dose PO studies in rats and dogs for up to 1 year, and in repeated-dose I.V. studies in rats, dogs, and monkeys for up to 1 month. The carcinogenic potential of the drug was evaluated in PO studies in mice (B6C3F1) and **two strains of rats** (Sprague-Dawley and Fischer-344). Additionally, studies to assess the **potential for tumor promotion** were conducted. Special toxicity studies of PANTO assessing pulmonary and thyroid effects, alteration of gastrin and cholesterol levels, effects on red blood cells (RBCs) (in vitro), effects in combination with antibiotics, mitogenicity, and antigenicity were conducted. Irritation potential of the drug after intramuscular (IM), dermal, I.V., intra-arterial, paravenous, and ocular administration was evaluated. PANTO was evaluated in fertility and general reproductive performance studies in rats, developmental toxicity studies in rats and rabbits, and perinatal and postnatal development studies in rats. The mutagenic potential of this PPI was evaluated in an extensive battery of in vitro and in vivo assays. Additional toxicity studies were conducted with ———————— (a manufacturing impurity and degradation product), the thiol metabolite of pantoprazole, and the (+)- and (-)-enantiomers of pantoprazole. In addition, studies to determine the single- and repeated-dose pharmacokinetics of PANTO were conducted in mice, rats, dogs, and monkeys. Tissue distribution (rats and monkeys), protein binding (mice, rats, and dogs), metabolism (rats, dogs, and monkeys), and excretion (mice, rats, dogs, and monkeys) were also studied. The effect of this PPI on hepatic drug-metabolizing enzymes was assessed in rats and dogs. In addition, studies in rats and dogs were conducted for PK evaluation of PANTO in combination with antibiotics.

Listed below are the main findings from these nonclinical evaluations, followed by a brief comment on clinical relevance or conclusions based on human data.

- Decreased RBC parameters were observed at high dosages in repeated-dose studies, mainly in rats.

  → Decreased RBC parameters were observed at high dosages in repeated-dose studies, mainly in rats.

  → These observations are not considered clinically relevant, because concentrations of blood achieved with therapeutic exposure in humans is not expected to be as high as that seen in animals experiencing RBC hemolysis. In addition, the safety database have not revealed effects on RBC parameters.

- Increased cholesterol levels were observed in rats in the 12-month PO study and in dogs in the 6- and 12-month PO studies.

  →The increase was associated with the HDL fraction in the 12-month dog study. In another study, a high PANTO dosage of 300 mg/Kg/day increased cholesterol (up to 66%) in rats.

- Pulmonary edema in repeated-dose studies in dogs is considered to be caused by the **third** metabolite of pantoprazole.

  →This metabolite has not been found in humans; the occurrence of pulmonary edema in dogs seems to be without clinical relevance.

- Administration of PANTO (and other PPIs) led to increased gastrin production in rats and dogs. These are expected findings, known to be secondary to inhibition of gastric acid secretion (the intended pharmacologic action of PANTO) leading to increased gastrin levels and "an associated proliferation of gastric cells".

  → Although it is true that, regardless of the PPI, profound inhibition of acid secretion leads to hypergastrinemia, not all instances of epithelial cell proliferation (i.e. EC-like cell hyperplasia, etc.) are accompanied by hypergastrinemia. The reviewer believes that other cell proliferation peptides, with para- or autocrine effects, which have not been well characterized, may also contribute to the observed gastric cell proliferation in animals (and humans) following PPI administration.

- Increased liver weight, enzyme induction, and hepatocellular hypertrophy were seen in repeated-dose studies in rats and dogs.

  → In reality, the relevance of these animals findings to humans is not known. The sponsor claims that "in clinical trials, changes in liver function parameters (ie. serum AP, BIL, ALT, AST) were infrequent and slight and were not considered clinically relevant".

- Thyroid changes (ie, increased thyroid weight and/or follicular cell hypertrophy) observed in repeated-dose studies in rats and dogs are considered secondary to effects on the liver. Changes in thyroid hormone metabolism (increased biliary T_4 elimination, decreased T_3, increased TSH) and hepatic phase-II enzyme induction (increased UDPGT activity) were observed with pantoprazole in rats. Similar findings with other PPI, such as omeprazole have been reported.

  → The reviewer agrees with the sponsor's statement that no clinically significant changes in thyroid function have been observed in humans.

- Three carcinogenicity studies were carried out with PANTO. In a mouse (B6C5F1) carcinogenicity study with PANTO at PO dosages of 5, 25 or 150 mg/Kg/day, tumors were observed in the liver. In the first (Sprague-Dawley) rat carcinogenicity study with PANTO at PO dosages of 0.5, 5, 50 or 200 mg/Kg/day, tumors were observed in the glandular stomach, forestomach, liver and thyroid. In the second (Fischer) rat carcinogenicity study with PANTO at PO dosages of 5, 15 or 50 mg/Kg/day, tumors were observed only in the glandular stomach.

  → According to the sponsor, in both rat carcinogenicity studies, characteristic target organ effect and tumors associated with this drug class were observed. In addition, a possible chief-cell adenocarcinoma in combination with an NE-cell tumor (at 200 mg/Kg/day), and adenomatous polyps (at 200 mg/Kg/day) were considered to be induced by the trophic effects of gastrin. The latter tumors are not relevant to humans because there is no forestomach in humans and PANTO is expected to by-pass the stomach because it is administered as enteric coated tablets. The former type of tumors (NE-cell) have not been observed in humans under conditions of therapeutic exposure. It is claimed that nongenotoxic mechanisms of rodent hepatocellular tumorigenesis is associated with cytochrome P_{450} enzyme induction at high doses leading to centrilobular hypertrophy and tumors in low incidence. The statement is made that hepatocellular tumors at high doses in rodents are not indicative of human carcinogenicity risk. It is also claimed that effects on the thyroid with PANTO are secondary to induction of liver uridine diphosphate glucuronyl transferase (UDPGT) leading to enhanced metabolism of thyroid hormones, increased TSH, and an eventual trophic effect on the thyroid.

[ ]

- Two studies (one examined the forestomach; the other the liver and thyroid) intended for detection of tumor promoting activity of PANTO were conducted in Sprague-Dawley rats.

  → Both studies were considered inadequate for assessment of tumor promotion.

- In studies to elucidate the nature of the hyperplastic and hypertrophic response in the rat liver and to assess the potential for DNA damage in the rat liver, PO (gavage) dosages of PANTO, OME, and LANSO were administered for 4 weeks. The dosage of pantoprazole (200 mg/Kg/day) was the same as the highest dosage in the rat carcinogenicity studies. The low dosages of OME and LANSO were the same as the PANTO dosage; additional higher dosage groups were included for the other two PPIs in order to give exposure (AUCs) in plasma similar to that with 200 mg/Kg/day of PANTO. The sponsor concluded that **there was no evidence of increased hepatic DNA adduct formation.**

→ These results seem to show that the reversible hepatic effects (increased liver weight, hepatocellular hyperplasia, and hypertrophy) of the three PPIs in rats are qualitatively similar. The sponsor proposes that minor quantitative differences are attributable to differences in dosage levels and systemic exposure to the compounds.

- In an extensive battery of in vitro and in vivo genotoxicity assays, PANTO was negative in the following in vitro assays:

  Microbial mutagenicity
  CHO AS52 GPT
  mouse lymphoma
  unscheduled DNA synthesis, and
  cell transformation in C3H mouse M2 fibroblasts and
  Syrian hamster embryo cells.

  - PANTO was also negative in the in vivo chromosomal aberration assay in rat bone marrow.

  - PANTO was positive in the **in vitro chromosomal aberration assay in human lymphocytes**; LANSO and OME were also positive in this assay.

  - In the *in vitro* CHO/HPRT mammalian forward gene mutation assay, increased in mutation frequency were considered to represent normal assay variability because they were below the pre-established criterion for a positive response and there was lack of a dose response.

  - In the DNA binding study in rat liver (ex vivo), the small amount of binding was not considered biologically relevant because the radioactivity level was low and no distinct radioactive peaks were seen; this evaluation was further supported by results of a mechanistic study in which there was no increased hepatic DNA adduct formation with PANTO.

  - Two *in vivo* mouse micronucleus studies were carried out. In the first, increases in the number of micronucleated PCEs were considered to be due to chance variation because the statistically significant results were comparable to historical controls; in the second more extensive study, there was no increase in micronucleated PCEs and, therefore, PANTO was considered negative in this test system.

  → PANTO was negative in all of these tests of mutagenicity/genotoxicity, except the *in vitro* chromosomal aberration assay in human lymphocytes. However, according to the sponsor, the two PPIs approved for L-T use, omeprazole and lansoprazole, were also positive in this assay.

- PANTO was not teratogenic in rats or rabbits and did not affect fertility in rats.