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at or below the predetermined primary efficacy endpoint. The only time period without appropriate control was at month 3, particularly in MEN-1 patients. The majority of treated patients were controlled with the initial oral pantoprazole dose of 40 mg bid or by adjustment to a higher 80 mg bid dose. Five patients required the maximum allotted 240 mg pantoprazole daily dose. Byk Gulden study FK3038 enrolled 11 patients; 10 in South Africa and 1 in Belgium. Ages ranged from 27-74 y (6 South African Black -1 African Indian - 4 White). Ten patients had ZES and one had MEN-1. Oral pantoprazole treatment at doses of 40-80 mg/d and up to 160 mg/d controlled BAOs. However, control of BAOs was inconsistent in the first months (up to month 6), and pantoprazole mean required doses for individual BAO control were, overall, higher than in study 307-US. The reasons for these differences in pantoprazole responses are unclear.

2.3 Safety.

There were relatively few serious AEs, and the majority were *not* considered by the investigators, or by this reviewer, related to the administration of oral pantoprazole. Deaths (5 in W-AR 307-US and 2 in FK3038) were probably due to worsening of underlying neoplasms. During the experimental period of pantoprazole treatment, 5 ZES patients in the FK3038 study developed gastric ECL-cell hyperplasia, and 1 developed gastric dysplasia. ECL-cell hyperplasia may be a precursor of carcinoids. None of the patients developed carcinoids during the trial, and serum gastrin concentrations, the stimulus for ECL-hyperplasia, were not increased during the treatment period.

2.4. Dosing, Regimen and Administration.

The sponsor's proposed pantoprazole dose regimen, starting with a dose of 40 mg bid, and adjusting as required by gastric BAOs, is acceptable.

2.5. Drug-Drug Interactions

The approved and marketed W-AR label for oral PROTONIX® tablets has a section of drug-drug interactions. No new amendments to that label section are recommended.

2.6. Special Populations.

The submitted pivotal US studies included a rather small patient population (35). The majority of patients were under 27 years of age and white (32). No conclusions on special adult populations can be drawn from the submitted pivotal US study. ZES is extremely rare in pediatric populations younger than 16 years of age.

II. The Clinical Review

1. Introduction and Background.

1.1 Proposed Indication and Dose [taken from the electronic document (ed)].

INDICATION. “PROTONIX Delayed-Release Tablets are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome”.

DOSE. The dosage of PROTONIX in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult starting dose is 40 mg twice daily. Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered. Some patients have been treated continuously with PROTONIX for more than 2 years.

1.2 State of Armamentarium for Indication.

Zollinger-Ellison Syndrome (ZES) is characterized by high gastric basal acid output (BAO), i.e., gastric hypersecretion induced by gastrin-producing tumors located in the pancreas or the duodenum (gastrinomas). ZES may be associated with multiple endocrine neoplasias (MEN-1). The continuous gastric acid hypersecretion leads to the development of multiple gastric and duodenal ulcers, and acid-induced diarrhea. Treatment of ZES is directed towards control of gastric acid hypersecretion by gastric acid inhibitors, such as H₂-receptor antagonists (H₂-Blockers) and the more powerful Proton-Pump Inhibitors (PPIs), including pantoprazole.

The next chronology lists H₂-blockers and PPI oral formulations approved for the treatment of ZES and pathological gastric hypersecretory states:

H₂-Blockers

- Cimetidine (TAGAMET[®]) tablets, administered in doses 300 mg four a times a day, or in doses adjusted to individual patients up to 2400 mg/d, is approved for “*the treatment of pathological hypersecretory conditions (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas)*”.
- Ranitidine (ZANTAC[®]) tablets, administered in doses of 150 mg twice a day, or in doses adjusted to individual patients up to 6 g/d, is approved for “*the treatment of pathological hypersecretory conditions (e.g., ZES and systemic mastocytosis)*”.
- Famotidine (PEPCID[®]) tablets, administered in doses adjusted to the individual patient, 20 mg q6/h up to 160 mg q6/h, is approved for “*the treatment of pathological hypersecretory conditions (e.g., ZES, multiple endocrine adenomas)*”.

PPIs

- Omeprazole (PRILOSEC®) delayed-release capsules, in a starting dose of 60 mg/d and in doses up to 120 mg t.i.d., is approved for *"the long-term treatment of pathological hypersecretory conditions (e.g., ZES, multiple endocrine adenomas and systemic mastocytosis)"*.
- Lansoprazole (PREVACID®) delayed-release capsules, in a starting dose of 60 mg/d, and in doses up to 90 mg bid, is approved for *"the long-term treatment of pathological hypersecretory conditions, including ZES"*.
- Rabeprazole (ACIPHEX®), delayed-release tablets, in a starting dose of 60 mg/d, and in doses up to 120 mg/d, is approved for *"the long-term treatment of pathological hypersecretory conditions, including ZES"*.

Gastric acid hypersecretion may occur in a number of conditions in which there is no apparent gastric pathology or associated increase in gastrin serum concentrations, e.g., short bowel syndrome. A very rare systemic malignancy, i.e., systemic mastocytosis, may induce gastric acid hypersecretion via increase histamine production. The following table, (*Chapter on Treatment of ZES and other Gastric Hypersecretory States; Therapy of Digestive Diseases, Editor: Michael Wolf et al, Saunders, 2000*), lists all the conditions which have associated gastric acid hypersecretion.

TABLE 1

**Etiologic Classification of Gastric
Hypersecretory States**

A. Associated with hypergastrinemia
1. Retained gastric antrum syndrome
2. Antral G-cell hyperplasia/hyperfunction
3. <i>Helicobacter pylori</i> infection
4. Gastric outlet obstruction
5. Short-bowel syndrome
6. ZES
7. Chronic renal failure (rare)
B. Associated with hyperhistaminemia
1. Systemic mastocytosis
2. Basophilic granulocytic leukemia
C. Unknown etiology
1. Idiopathic hypersecretion
2. Associated with non-gastrin-secreting tumor (non-ZES tumor)
3. Possible association with gastric hypersecretory states
a. Hypertrophic, hypersecretory gastropathy
b. Associated with stress
c. Associated with head lesions
d. Cystic fibrosis
ZES, Zollinger-Ellison syndrome.

1.3 Product Development

The program to develop oral pantoprazole tablets was first submitted to this Agency by _____ on September 13, 1990. The application was placed on clinical hold because pre-clinical data did not support the safety of the proposed doses and the drug exhibited mutagenic effects. The sponsorship of _____ was first transferred from _____ to Byk Gulden Lomberg (GmbH) in 1992 and then to W-AR on June 5, 1996. W-AR submitted a complete response to the clinical hold letter and amendments dated June 7, June 18, 1996. In its response, W-AR claimed that the safety profile of pantoprazole is comparable to the omeprazole and lansoprazole safety profiles (approved drugs of the same class). W-AR pre-clinical data was fully reviewed by the CAC. The DGICDP met with W-AR on July 10 and October 8, 1996. As a result of these discussions, on October 15, 1996 the clinical hold was lifted for Protocols 300 and 301 (acute treatment of erosive esophagitis or EE). Subsequently, on December 13, 1996, the clinical hold was also lifted for Protocols 302 and 303 (maintenance of healed EE).

1.4 Foreign Drug Marketing and Presently Approved Indications for Protonix Use in the USA

Oral pantoprazole was first approved by regulatory authorities in Germany and South Africa. Since 1994, it has been marketed under the trade names Pantoloc, Pantozol, and Rifun in Germany, and Controloc and Pantoloc in South Africa. In Germany, pantoprazole tablets are approved for the treatment of duodenal ulcer (DU), gastric ulcer (GU), and reflux esophagitis (GERD, stages 2 and 3). In South Africa, the approved indications are the same with no stage limitation for use in reflux esophagitis. As of February 23, 2001, Byk Gulden, Germany, and its licensees and partners, marketed oral pantoprazole 40-mg tablets in 82 countries and 20-mg tablets in 37 countries. Pantoprazole oral tablets are approved for the indication of ZES in 19 foreign countries. In Australia and Mexico, the labels for use in ZES patients, recommend adjusting the pantoprazole oral dose to maintain a gastric acid output below 10 mmol/L.

In the USA, pantoprazole oral tablets are approved for the following indications:

- *Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD)*
- *Maintenance of Healing of Erosive Esophagitis*

On October 19th, 2001, the DGICDP approved the use of the intravenous formulation of PROTONIX[®], for the *treatment of pathological hypersecretion associated with Zollinger-Ellison Syndrome or other neoplastic conditions.*

1.5. Present Postmarketing Commitments.

The only relevant clinical post-marketing commitment relates to the sponsor's agreement that occur during the approval process of PROTONIX[®] tablets for the indication of maintenance of healed erosive esophagitis (NDA 20-987/S001). As part of the approval of this first maintenance indication of PROTONIX[®], W-AR agreed to a post-marketing commitment to conduct a long-term prospective observational study on the incidence of cancer among pantoprazole users, compared to an appropriate control group. As initial implementation of the agreement, Wyeth submitted a draft protocol on September 12, 2001. On October 19, 2001, representatives from Wyeth and this Agency discussed the merits of the protocol in a teleconference. The following basic decisions achieved from the teleconference were summarized in the Division's:

- (a) Wyeth is not required to initiate the agreed post-marketing study within 6 months of the NDA 20-987/S001 approval (December 12, 2001). The rationale for this decision was the need of further revision of the protocol.
- (b) FDA will renegotiate the timeline for initiation of the post-marketing study.

In a follow-up letter dated *December 21, 2001*, the deadlines for submission of the amended protocol for *Long-Term Prospective Observational Study of the Incidence of Cancer Among Pantoprazole Users Compared to an Appropriate Control Group*, and commencement of the study were re-established, as listed below:

Revised Protocol Submission	→ Within 3 months of 12/21/2001
Study Start	→ Within 6 months of 12/21/2001
Progress Report(s)	→ First report within 1 ½ year of 12/21/2001
Final Report submission	→ Within 10 ½ years of 12/21/2001

2. Class of Drug and Pharmacology Issues.

(a) Pantoprazole is a substituted benzimidazole. It inhibits gastric acid by non-competitively binding to the H⁺K⁺ATPase in the specialized acid-producing gastric cells (parietal cells). ATPases have the general function of creating energy by releasing covalently bond phosphates from a specific phosphate substrate, i.e., Adenyl Tri Phosphates (ATP). As source of energy or fuel, ATPases function as "pumps". In the stomach, the specific action of the H⁺K⁺ATPase is to "pump" protons into the secretory canaliculi of the parietal cells. The acid milieu of these canaliculi "activates" the PPI. Similar to previously approved PPIs, the activated pantoprazole then binds to the gastric H⁺K⁺ATPase "proton pump", inhibiting the enzymatic action. The inhibition is mediated by the sulfur group of the pantoprazole moiety. Thorough its sulfur site, pantoprazole binds to thiol groups of the H⁺K⁺ATPase forming an irreversible covalent disulfide bond.

(b) After intestinal absorption, pantoprazole is partly metabolized by the liver CYP450 oxidizing enzymes, largely by CYP2C19, and to minor extent by CYPs3A4, 2C9, 2D6.

Its major metabolite was designated M2. The genetic pleomorphism of the CYP 2C19 influences the bioavailability of pantoprazole. Pantoprazole bioavailability is greater, up to 5 times, in the so-called "slow or poor metabolizers" (PMs). The prevalence of PMs is higher in Asians, e.g., Japanese, Chinese, Koreans.

The pharmacodynamic (PD) action of pantoprazole (gastric acid inhibition), as well as all the PD of the other PPIs, is dependent upon an equilibrium between the blood-circulating pantoprazole and the available parietal cell ATPases. The half-life of circulating pantoprazole ranges from 1-2 hours. The first pantoprazole dose will bind in an irreversible link to the available cell ATPases. Since the ATPase turnover is 50 hours, only 25% of ATPase will be renewed, and available every 24 hours. This may explain the lack of linearity at doses higher than 40 mg doses, as shown in the next table, *scanned unmodified from the approved pantoprazole label*:

Effect of Single Daily Doses of Oral Pantoprazole on Intra-gastric pH				
	----- Median pH on day 7 -----			
Time	Placebo	20 mg	40 mg	80 mg
8 a.m. - 8 a.m. (24 hours)	1.3	2.8*	3.6**	3.9**
8 a.m. - 10 p.m. (Daytime)	1.6	3.2*	4.4**	4.6**
10 p.m. - 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

* Significantly different from placebo
 ** Significantly different from 20 mg

The almost unavailable cell ATPase after exposure of the enzyme to initial pantoprazole doses, appears to explain the lack of dose-linearity in normals, but fails to explain the PD linearity to very high pantoprazole doses observed in ZES. It is possible that the increase parietal cell mass in ZES compensates for the slow ATPase turnover.

3. Toxicology: Experimental Carcinogenesis

The pantoprazole genotoxicity shown in experimental Sprague-Dawley rats treated for 24 months with doses up to 200 mg/kg/day is of continuous concern. All PPIs induce ECL hyperplasia and carcinoids in a dose-related manner. The development of gastric adenocarcinomas is rare. Of the *previous PPIs, doses up to 352 times the human dose* (based on a patient weight of 50 kg and a dose of 20 mg) resulted in the development of a *single malignant gastric carcinoma* in one rat. The omeprazole label states that this is an *unusual malignant primary tumor in the stomach of the rat*. In the pantoprazole Sprague-Dawley experiments, *doses 10-40 times the recommended human dose resulted in the development of malignant cell squamous cell carcinomas in the stomach, an adenocarcinoma of the duodenum and an adenocarcinoma of the gastric fundus*. Subsequent experiments with p53 (+/-) transgenic mice, failed to reproduce the results observed in the Sprague-Dawley mice. Yet, a glioma was found in pantoprazole treated p53 (+/-) mice whereas was not found in p53 (+/-) mice treated with omeprazole or lansoprazole. Gliomas are rare in mice, with an incidence ranging from 0% to 0.006 %.

The incidence of gastric carcinoids in the overall human population is very low. In contrast, the finding of gastric carcinoids is not as uncommon in patients with ZES.

4. Sources of Clinical Information

4.1 Source of Clinical Data

The source of clinical data used to review safety and effectiveness of oral pantoprazole tablets in ZES was the submitted report of a pivotal trial conducted by W-AR in the US, and supportive trials conducted in foreign countries by Byk Gulden. The report of these clinical trials was submitted by W-AR electronically (edr), and in desk hard copies

4.2 Submitted Listing of Clinical Trials for the Proposed Indication

The following tables list the W-AR pivotal study 3001A1-307-US and the supportive By Gulden studies performed with the aim to determine safety and efficacy of pantoprazole oral tablets in the treatment of pathological hypersecretory states, including ZES.

TABLE OF STUDIES FOR ORAL PANTOPRAZOLE NDA FOR THE TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS, INCLUDING ZOLLINGER-ELLISON SYNDROME

Protocol No. (BG Report No.) W-AR Report No.	Study Dates	Study Design	Diagnosis / Criteria for Inclusion	Test Product / Reference Therapy	Dose, Route, Frequency, Duration	Number Enrolled in Study ^a	Sex, Age ^b Range; Mean or Median Race ^c
Primary Evidence of Safety and Efficacy							
W-AR Open-Label Study - Zollinger Ellison Syndrome							
3001A1-307-US CSR-37322	02/19/96 to 11/01/00 (data cut- off date)	OL, pantoprazole only, with dose adjustments of pantoprazole, if needed, to maintain acid output at less than 10 mEq/hr in ZES patients who have not undergone gastric reduction surgery or at less than 5 mEq/h in those patients who have undergone gastric acid reduction surgery.	Patients with ZES or other gastric hypersecretory conditions and documented basal acid output >15 mEq/h requiring pharmacological control.	Pantoprazole 40 mg to 80 mg tablets	The expected starting dose of pantoprazole was 40 mg oral BID. The order of titration was 40 mg BID, 80 mg BID, 120 mg BID, and 80 mg TID, orally if the starting dose selected was insufficient to control acid output. Based on data available from gastric acid output measurement on study day 6, the dosage was to be changed to the next dose.	35 P (26 patients with ZES and 9 patients with idiopathic gastric hyper- secretory conditions [IGH ¹])	22 M 13 F 30-74 Mean 51.7 3 B 32 W
Multicenter US							

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TABLE OF STUDIES FOR ORAL PANTOPRAZOLE sNDA FOR THE TREATMENT OF PATHOLOGICAL HYPERSECRETORY CONDITIONS, INCLUDING ZOLLINGER-ELLISON SYNDROME

Protocol No. (BG Report No.) W-AR Report No.	Study Dates	Study Design	Diagnosis Criteria for Inclusion	Test Product Reference Therapy	Dose, Route, Frequency, Duration	Number Enrolled in Study ^a	Sex, Age, Range; Mean or Median Race ^b
Investigator(s) Country							
FK3038 (R549) CSR-35236	10/95 to 11/98	OL, multinational study to evaluate the effects of doses of pantoprazole (starting dose of 40 daily; if necessary, upward titration, in 40 mg increments, to a maximum daily dose of 160 mg) on acid output (AO) in patients with ZES for up to 3 years.	Patients diagnosed with ZES according to: a) BAO >15 mmol/hour, b) elevated fasting serum gastrin >600 ng/L, and c) positive histological diagnosis of gastrinoma	Pantoprazole 40 mg tablets	Pantoprazole 40 mg QD for 5 days and the dose for patients who failed to achieve BAO <10 mmol/h was titrated to pantoprazole 40 mg BID tablets until day 9 and, if required, up to day 13. The dosage of pantoprazole was increased by 40 mg daily until a maximum dose of 160 mg up to 3 months.	11 P	8 M, 3 F 27-74 Median: 56
Multicenter South Africa Belgium							

An intravenous (iv) formulation of Protonix indicated for the acute treatment of pathological hypersecretory states, including ZES was approved on October 2001, under NDA 20988. The indication was supported by clinical data obtained in two multi-center clinical trials, 3001K1-304-US and 2001K1-308-US. Some of the patients who were enrolled in these studies and completed successfully the treatment, were enrolled in the pivotal trial 3001A-307 (submitted in this application) and treated with oral tablets.

4.3 Information from Postmarketing Experience.

- i. Spontaneous Postmarketing Reports of Serious Adverse Events. In this section of the submission, the sponsor notes that the spontaneous reports of serious AEs for the period covering August 24th 1994 through December 31st 1997 were included in NDA 20-987. Spontaneous reports for the period covering January 1st 1999 through December 31st 1999 were reported in sNDA 20-987/S-001. Spontaneous reports for the safety update to sNDA 20-987/S-001 for the period from January 1st 2000 through June 12th 2000 were included and reviewed in my review of this supplement (March 16th 2001).

W-AR now submits information of spontaneous serious AEs received during the period from June 12th 2000 to December 31st 2000. During this period, AEs were reported from 66 patients, 40 women and 25 men (sex was unavailable for 1 patient). Most of the patients received 40 mg pantoprazole/day. Twenty six patients were 65 years of age or older (age was not reported for 13 patients). The descriptive list of the 66 spontaneous AE reports was submitted by W-AR in Table 1.5.2A. The table includes one death of a cause not specified (NOS) with no report of patient's age, pantoprazole dose or length of pantoprazole therapy. The list also includes at least 2 non-accidental pantoprazole overdose cases, cases of anaphylactic shock reactions, and patients with moderate to severe liver abnormalities. W-AR notes that 47 of the cases had been submitted previously in INDs and NDAs safety reports. Overall, W-AR concluded that these data do not raise serious concerns regarding treatment with pantoprazole.

W-AR Table 1.5.2A, Spontaneous Postmarketing Serious AEs, June 12-December 31, 2000, is included as Appendix 1 of this review.

- ii. Reports of Serious AEs from Postmarketing Observational Studies. In the next Table 1.6A, the sponsor submitted a list of AEs which occurred in postmarketing observational studies reported from June 12th 2000 to December 31st 2000. W-AR notes that these AEs had not been submitted previously. Six serious AEs were reported from Byk Gulden in patients taking oral pantoprazole enrolled in observational studies. Two patients had cancer and 1 patient died. These AEs were not considered by the sponsor to be related to the pantoprazole treatment. W-AR concludes that these reports of AEs in observational studies do not raise concern over the safety profile of oral pantoprazole treatments.

TABLE 1.6A. PATIENTS WITH SERIOUS ADVERSE EVENTS IN OBSERVATIONAL STUDIES (BYK GILDEN)

W-AR Control Number Study-Patient Number	Adverse Event Detail Term ^a	Date Report was Received by Wyeth-Ayerst	Country ^b	Age (y)	Sex	Total Daily Dose	Therapy Duration (days)	Outcomes/ Action ^c
HQ0996214SEP2000	Sepsis NOS; stomatitis; diarrhoea NOS; neutropenia; colitis pseudomembranous	14 Sep 2000	GE	Unknown	M	Unknown	Unknown	D
HQ1594929SEP2000	Thrombocytopenia; petechiae	28 Jul 2000	US	72	F	Unknown	Unknown	R
HQ3780416NOV2000	breast neoplasm (NOS)	14 Nov 2000	GE	55	F	Unknown	Unknown	H
HQ9688910AUG2000	Pneumonia (NOS); urinary tract infection (NOS)	09 Aug 2000	BR	57	NR	40 mg/day	358 days	H
HQ9695110AUG2000	Gastric cancer (NOS)	24 Oct 2000	HU	46	F	Unknown	8 days	L

a. Adverse Event (AE) term according to MedDRA terminology.

b. Countries: BR = Brazil, GE = Germany, HU = Hungary, US = United States

c. Outcomes/Actions: D = died; H = hospitalized; L = life threatening; R = recovered.

4.3 Literature Review.

The sponsor submitted an extensive reference list of publications (146 references). This reference list cites publications on PPI dosing, metabolism, and use of pantoprazole and other PPIs in GERD, *Helicobacter pylori*, peptic ulcer, as well as a few references on pantoprazole and PPIs for ZES treatment. The W-AR database was obtained from Zmedline, Embase, Biosis and Derwent Drug File. This reviewer also consulted references from relevant gastroenterology books, PubMed, and a personal reference list.

5. Clinical Review Methods.

5.1 Sequence of the Review Process.

This review followed a stepwise methodology directed to determine the factual clinical evidence to support the sponsor's proposed label, i.e., use of oral pantoprazole tablets for the indication of pathological hypersecretory states including ZES. The US Pivotal Clinical Trial 307 was first examined; the reported data from this pivotal trial assessed for efficacy and safety. Effectiveness and safety of patients enrolled in supportive foreign small trials were subsequently evaluated. My final judgement on safety and effectiveness

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of pantoprazole tablets for the proposed indication was based on the proportion of serious ADEs, on whether the objectives of the prospective primary efficacy endpoints were achieved, and, on a rough estimate of the risk/benefit ratio. In my recommendations, I carefully balanced the benefit of the pantoprazole treatment (a PPI) upon the relevant pathophysiological (gastric acid hypersecretion) manifestation of gastrinomas, and the potential (though not proven in humans) of added carcinogenesis with pantoprazole use..

5.2 Overview of Materials Consulted in Review.

The main source of information for the review process was the clinical data submitted by the sponsor in the electronic document. This reviewer also consulted about 18 desk hard volumes. Out of these, the first 5 volumes were related to trials of pantoprazole in ZES. Volumes 1 and 4 had reports of patient disposition, efficacy and safety from US Pivotal Clinical Trial 307 and thus, they were examined in more detail. The submitted data were compared with previous data on oral pantoprazole for GERD (acute treatment and maintenance of healed esophagitis) and, with data submitted to support the intravenous use of pantoprazole for the treatment of acute pathological hypersecretory states, including ZES. Reviews on pantoprazole pharmacology, acute treatment of GERD and ZES, as well as reviews on pantoprazole use for maintenance of healed GERD, were consulted from the PROTONIX Action Package (or by copies of reviews obtained from MO reviewers). *In summary, the submitted data, previous pharmacology and clinical reviews, the statistical data, and the risk/benefit assessment were the basic consulting materials used during the process of this review.*

5.3 Data Quality and Integrity.

The present submission is a NDA supplement with only one trial (307US) conducted in the US. Most of the five principal investigators enlisted in this US trial participated in previous trials designed to assess safety and effectiveness of intravenous pantoprazole in ZES. Field inspections by the DSI to inspect facilities and records were conducted for the previous indication. No new field inspections were carried out for this supplement.

5.4 Ethical Standards.

The sponsor reports that all enrolled and treated patients signed a consent form. Standards in submitted clinical trials followed the recommendation contained in amended Declaration of Helsinki.

5.5 Financial Disclosure.

The sponsor submitted a completed FORM FDA 3454. A list of investigators participants in Study 307-US was provided and the paragraph (1) of the FORM 3454, certifying the sponsor has not entered into any financial arrangements with the listed clinical investigators, was checked and signed by the W-AR Senior Vice President – R & D, and the Vice President – R & D Finance.

6.0 Integrated Review of Efficacy.

6.1. Approach to Review Efficacy of Pantoprazole Oral Tablets in ZES.

Throughout the text of the submitted document, the sponsor (W-AR) highlighted Study 307-US as the pivotal trial to support the proposed indication, i.e., oral pantoprazole tablets for pathological hypersecretory states including ZES. This medical reviewer concentrated on the careful efficacy review of the 35 patients reported in pivotal Study 307-US. As shown in Section 4.2 of this review, the sponsor also submitted supportive data obtained by Byk Gulden in small studies performed in foreign countries. Byk Gulden study

Byk Gulden study FK3038 was conducted in South Africa and Belgium, enrolled 11 ZES patients. This review will include overall efficacy data reported from these studies.

6.2 Pivotal Study 307-US.

6.2.1 Protocol 3001A1-307-US.

The original protocol 3001A1-307-US was completed on December 2nd 1997. There were three subsequent amendments. Amendment I was incorporated on November 6th 1998. Amendment II was incorporated on March 9th 1999. Amendment III was incorporated on February 12th 2000.

- The following is a list of the relevant issues included in the prospective protocol

6.2.2 Title (copied unmodified from the edr)

A SAFETY AND EFFICACY STUDY OF LONG TERM ORAL ADMINISTRATION OF
PANTOPRAZOLE IN PATIENTS WITH ZOLLINGER-ELLISON SYNDROME
OR OTHER HYPERSECRETORY CONDITIONS

6.2.3 Study Design.

(paraphrased from the edr and unmodified)

Open label, *pantoprazole only*, multi-center, with dose-adjustments of pantoprazole (if needed) to maintain the basal acid gastric secretion below the established level in the primary efficacy endpoint.

6.2.4 Study Objective (copied unmodified from the edr).

To evaluate the safety and efficacy of long-term oral administration of pantoprazole in patients with ZES or other hypersecretory conditions.

6.2.5 Duration of Study.

Patients participated in the study for 3 years, but the protocol states that the *only data from the 6 month visit will be used to determine efficacy.*

6.2.6 Number of Patients.

The protocol planned for an enrollment of 25 patients. This sample size was based on the basis of clinical judgement and patient availability and not on statistical calculations.

6.2.7 Diagnosis of ZES and Pre-Study Screening Evaluation.

According to protocol, pre-screening included PE, routine blood and urine chemistries, chest x-ray, 12-Lead ECG, thyroid tests, UGI endoscopy, fasting serum gastrin. The following various combinations of diagnostic tests was used in the protocol as the criteria to confirm the diagnosis of ZES (*copied unmodified from the protocol's Attachment 3*):

- Basal Acid Output > 15 mEq/h in patients who have not had gastric surgery.
- Basal Acid Output > 5 mEq/h in patients with previous gastric surgery.
- Fasting serum gastrin concentration > 100 ng/L (>100 pg/mL) with a positive secretin test [normal < 100 pg/mL].
- Positive Calcium infusion test
- Histological evidence of gastrinoma

6.2.8 Drug Doses

The prospectively planned initial pantoprazole dose was 40 mg every 12 hours. The protocol allowed adjustment of the pantoprazole dose to 80 mg q/12h, and to 120 mg q/12h if by the 10th day of pantoprazole treatment the gastric basal acid output (BA) exceeded 10 mEq/h. According to the protocol, pantoprazole dose adjustment was allowed to be administered after the 1 hour collection of fasting gastric juice and determination of gastric BAO. Once the appropriate dose was achieved, the protocol allowed the investigator to decrease the drug dose based on BAO results and clinical judgement.

6.2.9 Study Visits for Efficacy Evaluation.

After the initial first visit, there were scheduled 4 visits in the first month of treatment (Days 6th, 10th, 14th, 28th). Next visits were prospectively planned for months 2, 3, and 6

(final visit for efficacy evaluation). Days 10th and 14th visit were supposed to be used *only* if there was a need to increase the pantoprazole dose.

6.3 Inclusion Criteria

The following are the relevant points:

- ≥ 18 year men, women who are not pregnant and not-lactating, and use acceptable contraceptive measures.
- Patients who have the established diagnosis of ZES as per criteria listed in part 6.2.7 of this review.
- Patients who participated in Protocols 3001K1-304-US and Protocol 3001K1-308, were treated acutely with the intravenous pantoprazole, sign a new IRB written consent form, are eligible for inclusion.
- Patients with hypersecretory conditions other than ZES with documentation of gastric BAO >15 mEq/h.

6.3.1 Exclusion Criteria

The following are the relevant exclusion criteria, copied unmodified from the electronically submitted study protocol:

Significant upper gastrointestinal disorder (other than ZES or gastric hypersecretory conditions).

Clinically significant gastrointestinal bleeding within the month before study start (study day -7) that resulted in a hemoglobin level less than 10 g/dl or required a blood transfusion.

Previous history of total gastrectomy. Previous history of partial gastrectomy, vagotomy, pyloroplasty, a simple closure of perforation and tumor excision will not preclude admission into this study.

Pyloric stenosis, persistent dysphagia resulting in inability to swallow solid food easily, achalasia, ulcerative colitis, and Crohn's disease.

Any clinically significant medical condition, e.g., unstable cardiovascular, respiratory, neurologic, psychiatric, renal, or hepatic condition, or surgical illness, that would interfere with the ability of the patient to complete the study.

Suggested or confirmed malignancy except for those tumors associated with ZES, MEN-1, or successfully resected basal or squamous cell skin cancer.

Patients requiring chemotherapy or radiotherapy within 1 month prior to study start (study day -7).

6.3.2 Primary Efficacy Endpoint.

brackets [] added by the reviewer

“The primary endpoint is the number of patients with acid output at less than 10 mEq/h for [a period of] one hour before [administering] the first dose of pantoprazole on day 6 (or if the dose was adjusted, on Day 10 or day 14) and, at 6 months. Patients whose acid output is controlled by Day 14 will continue in the protocol at their established regimen. On day 14, if a patient’s output is not controlled (acid output greater than or equal to 10 mEq/h) the patient will be considered a treatment failure. The patient is a treatment failure if the patient’s acid output can not be controlled at 240 mg per day at any time”.

6.3.3 Concomitant Drugs.

Pantoprazole was the only PPI allowed during the trial. Other PPIs, or H₂-Blockers were not allowed during the study. The antacid Riopan was allowed to control pain.

6.4 Efficacy Results

6.4.1 Patient Population and Disposition.

Thirty five patients received pantoprazole treatment. W-AR Tables 9.1A and 9.1B display patient groups according to diagnosis and dosage regimen at 6 months. Two patients discontinued the trial during the 6 months of the efficacy study. Patient 30791-0307, a 35 y old man with idiopathic gastric acid hypersecretion was withdrawn after 8 days of treatment. He received 40 mg pantoprazole bid, complained of vertigo, nausea and lethargy. The investigator considered the nausea and lethargy to be severe and possibly related to pantoprazole. Patient 30791-0308, a 37 y old man with idiopathic gastric acid hypersecretion took only the initial dose and withdrew from the study due to intolerance to the nasogastric tube. Six other patients were discontinued after the 6th month. These cases will be discussed in the safety section of this review

According to the report, 32 patients received treatment for 6 months. Fifteen patients were treated for a period of 6 months to 1 year (5 patients with pantoprazole 80 mg/d, 9 patients with pantoprazole 160 mg/d, and 1 patient received pantoprazole 240 mg/daily). Ten patients were treated for 1 ½ year to 2 years (seven with pantoprazole 80 mg/d and three with pantoprazole doses ranging from 160-240 mg/d).

TABLE 9.1A. POPULATION BASED
ON DIAGNOSIS

Population by Diagnosis	n ^a
All patients	35
Patients with sporadic ZES	21
Patients with ZES + MEN-1	5
Patients with idiopathic hypersecretory conditions	9

a: This is the total number of patients in each group. Note that individual efficacy calculations at a given time-point may be calculated for a smaller number of patients if 1 or more patients had missing or unevaluable data.

TABLE 9.1B. POPULATION BASED
ON DOSAGE REGIMEN AT 6 MONTHS

Population by Dosage Regimen	n ^a
All patients	35
40 mg BID	25
80 mg BID	8
120 mg BID	2

a: This is the total number of patients in each group. Note that individual efficacy calculations at a given time-point may be calculated for a smaller number of patients if 1 or more patients had missing or unevaluable data. Three (3) patients withdrew before the 6-month evaluation but received 40 mg BID throughout treatment.

4.2 Patient Demographics.

Enrolled patients ranged in age from 30 to 74 years and in weight from 46 kg to 125 kg. The mean age was lower in patients with MEN-1 (46 y) than in patients who had only gastrinomas ("spontaneous") ZES (52 y), or, had "idiopathic" gastric acid hypersecretion. Of the 35 patients, 13 were women and 22 were men; 32 were white and 3 were black. Twelve patients had gastric acid-reducing surgery. Seven had a partial vagotomy (1 during the study), 4 had a partial gastrectomy, and 1 had a Billroth procedure. Two patients had undergone a Whipple procedure to treat pancreatic or duodenal tumors.

All enrolled patients had prior treatment with PPIs; 27 received prior treatment with omeprazole and 8 had prior treatments with lansoprazole.

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6.4.2 Primary Efficacy Data. Rate of Responders

The decrease in BAO was almost universal in all patients regardless of the underlying cause of hypersecretion, i.e. sporadic ZES, MEN-1, "idiopathic" gastric acid hypersecretion. The decrease in acid gastric acid secretion was achieved at almost all time periods. The majority of patients ($\pm 70\%$) were controlled with the initial pantoprazole dose of 40 mg bid.

In the pre-study phase, most of the patients with "idiopathic" gastric acid hypersecretion were controlled by either other PPIs or by pantoprazole therapy. However, patients with ZES or MEN-1 had BAO levels above 5 mEq/h prior to day 1 of the trial. After entering the study, the mean BAO was generally below 5 mEq/h with the exception of the BAO at 3 months in patients with ZES associated with MEN-1. These results are shown in the next W-AR Table 9.2.2A.

TABLE 9.2.2A. AO RATES (mEq/h) BY DIAGNOSIS THROUGH MONTH 6

AO Collection Period	Diagnosis	n	Median	Mean	95 th Percentile	Maximum
Before day -14	Sporadic ZES	1	0.37	0.37	0.37	0.37
Hour -1	Sporadic ZES	20	0.975	5.7098	32.3375	42
	ZES with MEN-1	5	1.375	10.3	27.275	27.275
	Idiopathic Hypersecretors	9	2.6125	3.4108	9.0275	9.0275
Day 1	Sporadic ZES	1	0.175	0.175	0.175	0.175
Days 2 to 4	Sporadic ZES	21	1.025	2.9726	9.075	27
	ZES with MEN-1	5	1.525	2.6	5.25	5.25
	Idiopathic Hypersecretors	8	0.9	1.5275	6.1025	6.1025
Days 5 to 7	Sporadic ZES	21	2.225	2.5464	6.925	14.15
	ZES with MEN-1	5	0.625	2.28	6.675	6.675
	Idiopathic Hypersecretors	8	1.2475	1.2313	2.625	2.625
Day 28	Sporadic ZES	21	1.325	1.5607	4.45	4.525
	ZES with MEN-1	5	0.5	2.08	5.4	5.4
	Idiopathic Hypersecretors	7	1.175	0.9721	2.175	2.175
Month 3	Sporadic ZES	21	0.625	2.371	8.95	18.6125
	ZES with MEN-1	5	0.825	10.185	39.875	39.875
	Idiopathic Hypersecretors	7	0.0675	0.8979	2.8	2.8
Month 6	Sporadic ZES	21	1.35	2.3774	8.875	10.45
	ZES with MEN-1	5	2.325	2.925	6.475	6.475
	Idiopathic Hypersecretors	6	0.11538	1.201	6.35	6.35

Most of the patients had gastric BAOs ≤ 5 mEq/h with pantoprazole doses of 40 mg (22-24 patients) or 80 mg (8 patients). At month 3, 2 patients required doses of pantoprazole higher than 120 mg. These results are shown in W-AR Table 9.2.2B.

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TABLE 9.2.2B - AO RATES (mEq/h) BY DOSAGE REGIMEN THROUGH MONTH 6

AO Collection Period	Dose	n	Median	Mean	Percentile ^{95th}	Maximum
Before day -14	40 mg BID	1	0.37	0.37	0.37	0.37
Hour -1	40 mg BID	24	1.4175	6.3695	27.275	42
	80 mg BID	8	1.4375	2.5563	9.975	9.975
	120 mg BID	2	11.5375	11.5375	22.675	22.675
Day 1	40 mg BID	1	0.175	0.175	0.175	0.175
Days 2 to 4	40 mg BID	24	0.55	1.3904	5.425	6.1025
	80 mg BID	8	2.5	5.9031	27	27
	120 mg BID	2	3.525	3.525	4.075	4.075
Days 5 to 7	40 mg BID	24	0.7125	1.5021	4.725	6.925
	80 mg BID	8	2.575	4.0875	14.15	14.15
	120 mg BID	2	2.9875	2.9875	3.05	3.05
Day 28	40 mg BID	23	1.175	1.5622	4.525	5.4
	80 mg BID	8	0.875	1.1875	3.175	3.175
	120 mg BID	2	2.275	2.275	2.8	2.8
Month 3	40 mg BID	23	0.625	3.488	9.45	39.875
	80 mg BID	8	0.375	0.9109	2.4875	2.4875
	120 mg BID	2	9.7438	9.7438	18.6125	18.6125
Month 6	40 mg BID	22	0.775	2.248	8.875	10.45
	80 mg BID	8	1.3875	1.9563	6.35	6.35
	120 mg BID	2	3.325	3.325	5.45	5.45

The sponsor included the narratives of 9 patients who, at times during the total 3 year study period, had BAOs which were unstable and difficult to control, and, of patients (5) who required a maximum dose of 240 mg pantoprazole. The narratives of these patients will be included as an appendix.

- *Narratives of patients who needed periodic individual adjustments of BAOs, or required the maximum dose of 240 mg/d, Pages 52-54 of the submitted efficacy section, are included as Appendix 1 of this review.*

6.4.3. Sponsor's Conclusion on Efficacy. (taken unedited from the ed).

- AO rates were controlled for most patients at all time points up to 6 months, regardless of diagnosis or dosage regimen. At 6 months, 94% of patients were responders.
- A majority of patients (57% at 6 months) obtained AO control at dosages of 40 mg BID.
- Ten (10, 31%) patients received dosage regimens of 80 mg or 120 mg BID at the 6-month evaluation to control AO.
- Dose adjustment, either to improve response or because of adverse events, was required for 11 patients. Average AO rates for 9 patients exceeded the efficacy criteria for AO control at various time points. Of these 9 patients, control of AO was achieved for 8 patients, by dose adjustment for 7 patients and without dose adjustment for 1 patient. Control of AO was achieved in all patients whose dose was adjusted.

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6.4.3 Reviewer Comments.

- This reviewer concurs with most of the sponsor's conclusion on efficacy. The efficacy results met the pre-established primary efficacy objective, i.e., sustained decrease of gastric BAO < 5 mEq/h, particularly in patients with a diagnosis of "sporadic" ZES and "idiopathic" gastric acid hypersecretory states. The BAO from some patients affected with multiple endocrine neoplasias (MEN-1) was uncontrolled at least in one of the scheduled visits, i.e., month 3. Yet, these patients have often associated parathyroid tumors and serum hypercalcemia. Hypercalcemia is known to stimulate gastric acid secretion. The cumulative addition of gastrin-secreting tumors and hypercalcemia renders these MEN-1 patients more refractory to control of their high gastric BAO by PPIs, including pantoprazole.
- A general critic of experimental drug trials conducted in ZES patients, not restricted to this pantoprazole study, is the absence, *in the efficacy section*, of information on the patient symptoms before entering the study, and during the experimental drug therapy (*it should be noted that TAGAMET ZES trials did include symptoms as efficacy parameters*). Though it is accepted that control of high BAOs is an appropriate surrogate of primary efficacy in ZES, it would still be relevant and educational to determine the proportion of ZES and MEN-1 patients who benefit from the gastric BAO control as relates to pain and abdominal discomfort. Any complications such as copious diarrheas, gastrointestinal bleeding, new ulcers, ulcer perforation, are clearly of relevance and were included in the safety section. However, prevention of symptom worsening, and ZES complications could have been included as secondary efficacy endpoints, since the principal aim in the use of PPIs is to prevent development of serious complications and worsening of symptoms.
- It should be noted that the gastric BAOs from nine patients entered with a diagnosis of "idiopathic hypersecretion" were already controlled by other PPIs or pantoprazole at baseline, before starting study therapy, i.e., baseline -1 hour mean BAO was 3.4 mEq/h in idiopathic hypersecretors. Hence, they did not meet the pre-established *Inclusion Criteria*. Further, the sponsor did not provide a pathology underlying reason for their gastric acid hypersecretion, e.g., mastocytosis, short bowel syndrome, which might have qualify them as supportive data for the proposed label of "pathological" hypersecretion.

6.5 Byk Gulden Study

As supportive studies, the sponsor submitted data on the use of pantoprazole in ZES and MEN-1 obtained in foreign countries. The two studies, — and FK3038 (BY1023) were designed and conducted by Byk Gulden and each enrolled 11 patients. The only relevant study that may support (or not) the proposed W-AR label is study FK3038.

In contrast, FK3038 was designed as a pantoprazole dose adjustment study in which ZES and MEN-1 patients were entered with gastric BAOs >15 mmoles (mEq)/h, treated and followed for at least 3 months, and in some cases for 10 months and 36 months. In this section, I will provide a very brief summary descriptive of the Byk Gulden FK3038 study and a relevant patient narrative.

6.5.1 Brief Summary Paragraph of Byk Gulden Protocol FK3038.

Byk Gulden Protocol FK3038, July 1995 was Titled "*Multi-National, Multi-Center, Open, Dose-Titration of Pantoprazole in Patients with ZES*". Eligible patients required a diagnosis of ZES, gastric BAO >15 mmol/h, a gastrin of ≥ 600 ng/dl, or >300 ng/dl after calcium or secretin stimulation. Exclusion criteria were similar as those described for W-AR Protocol 307-US. Since patients were supposed to have a ZES diagnosis and pre-treated with PPIs or H₂-Blockers (1 patient), the design included a 5 day pre-study washout period, 9-13 day dose titration period, and a 3 year maintenance period. The protocol planned a multi-center enrollment of 50 ZES patients. The primary efficacy was control of gastric BAO <10 mmol/h 24 hours. The initial pantoprazole dose was set at 40 mg/d and the highest at 120 mg/d. Upper GI endoscopies and serum gastrin levels were scheduled at entry and at various times during the maintenance period.

6.5.2 Summary of Relevant Efficacy Data Obtained in Study FK3038.

- *This study was conducted between 10/95 and 11/98.*

The Byk Gulden report 85/99 states that 11 ZES patients were enrolled in two countries, i.e., South Africa (10) and Belgium (1). Ten patients had a diagnosis of ZES and 1 patient had a diagnosis of ZES and MEN-1 Patient #1). Eight of the patients were females and 3 males. Mean age was 56 years (27-74). Five patients had a history of prior gastric acid-reducing surgery such as vagotomy or antrectomy (1).

Five patients did not complete the trial because of the following reasons:

- One patient did not tolerate the NGG tube (patient #2)
- Two patients had complete resolution of the ZES after ablation of gastrinomas.
- Two patients died (gastrin levels, histologies and deaths will be included in the safety section of this review)

Nine patients had endoscopies at entry, with the following endoscopic findings:

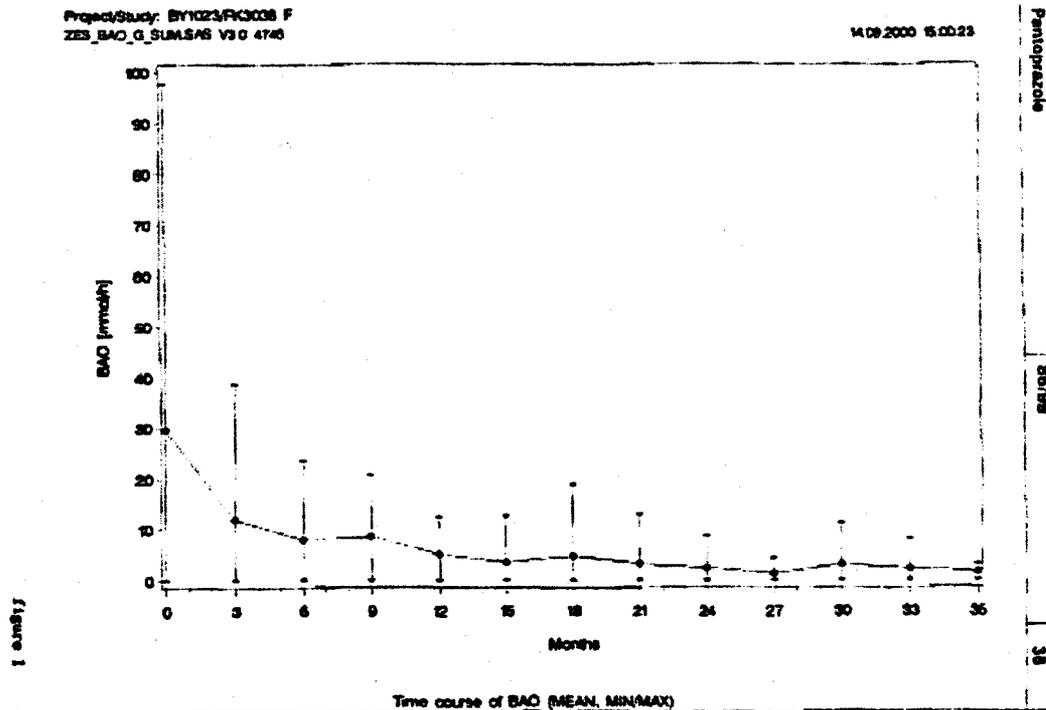
- Seven patients had "healed" endoscopies at entry, and two had either duodenitis or gastritis (the report indicates a patient with an esophageal ulcer but is unclear whether the ulcer was diagnosed at entry or in a second endoscopy).

At least 4 patients required doses of pantoprazole ranging from 80 mg/d to 120-160 mg/d to control the gastric BAO below the proposed 10 mmol/h.

The sponsor reports that treatment with pantoprazole decreased gastric BAOs from an average 29.7 mmol/h to 11.9 mmol/h at 3 months, and below 10 mmol/h in all subsequent months. The data are shown in the following Byk Guldea Table 4 and Figure 1.

Time course of BAO (mmol/h), Summary Statistics

Months	N	Mean	SD	Min	Max
0	11	29.66	29.64	0.00	97.80
3	11	11.85	13.93	0.00	38.63
6	10	7.82	9.05	0.00	23.43
9	10	8.63	8.32	0.00	20.71
12	9	5.09	5.57	0.00	12.46
15	9	3.44	5.00	0.00	12.50
18	7	4.66	7.07	0.00	18.81
21	6	3.17	4.86	0.00	12.88
24	6	2.34	3.24	0.00	8.73
27	6	1.24	1.63	0.00	4.34
30	6	3.05	4.19	0.00	11.16
33	6	2.19	2.98	0.00	8.00
36	2	1.60	2.26	0.00	3.20



The following are relevant parts from the narrative of patient #5:

74 y man enrolled with a pre-study BAO of 10.4 mmol/h. A secretin test performed led to the diagnosis of ZES based on pre/post serum gastrin concentrations. Due to bleeding the patient had a vagotomy + antrectomy in 1985. Endoscopy at entry showed minimal erosions in the stomach and duodenitis. The patients was treated with 40 mg pantoprazole in the maintenance phase and the BAO reduced to <5 mmol/h. The report states that "it is noteworthy that heartburn and gastric ulceration occurred despite a BAO of <5 mmol/h."

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6.5.3 Reviewer Comments.

As in the W-AR 307-US study, treatment with oral pantoprazole tablets controlled the gastric BAOs of the enrolled ZES patients. Efficacy was not evident, however, until the 6th month of pantoprazole therapy, and, BAO control < 10 mEq/h required high doses of 80 mg/d to 160 mg/d pantoprazole in 40% (4/10) of patients still remaining on month 6. The reasons for the delay in achieving control of the BAOs in this mostly South African trial are unclear but it might be related to the different racial composition of the patient population, i.e., 6 South African Black, and one African Indigenous. Hence, it appears that rapidity of BAO control to oral pantoprazole in ZES may not be uniform, at least in some populations, and may require more prolonged periods to achieve BAO control.

7.0 Integrated Review of Safety.

7.1 Material Utilized in the Review.

The summary data presented in this section of the review will include safety information from two sources, namely (a) Safety Data from Pivotal Trial 307-US, (b) Safety Data from Byk Gulden FK3038.. Each section will be presented separately. Subsequently to the descriptive of *both* studies, *I will, if needed, include a very brief section of comments.*

7.2 Safety Data from Pivotal Study 307-US.

For Pivotal Study 307-US, W-AR submitted safety information for visits up to November 1, 2000.

7.2.1 Deaths.

Five patients (30790-0305, 30791-0301, 30791-0304, 30791-0315 and 30791-0316) died during the study period. W-AR report that fatal events were considered to be unrelated to treatment with the study drug. The following are narratives of these fatal cases:

- 30790-0305; 32 y old black woman who began treatment with pantoprazole 80 mg bid on May 27th 1998. The dosage was increased to 120 mg bid at month 3. Primary diagnoses were ZES, Cushing's syndrome and gallstones. A pancreatic carcinoid tumor was diagnosed on 1993. She had bilateral adrenalectomy in 1994 because of metastasis. Her medications included sandostatin, interferon, florine, hydrosone AM and PM, oxycontin, digoxin,. On 9/24/00, she was admitted because of fever, chills, increased abdominal pain, diarrhea and CHF. Subsequently, she was placed in home hospice for terminal pancreatic cancer and died on Nov 21st, 2000.

- 30790-0301; 54 y white old female treated with pantoprazole 40 mg bid from May 5th 1998 until December 29th. On December 28th 1998, she was admitted to the hospital because of an altered mental status and was later found to be septic. Patient developed anuria with increase in serum creatinine (0.3 mg/dl on admission to 2.8 mg/dl). The patient had a history of alcohol abuse. Medications during the course of the trial included dopamine, flagyl, nystatin, cetizoxime, diflucan, gentamicin, vancomycin, vitamin K and thiamine. The sepsis probably developed as a consequence of acute tubular necrosis. The patient was transferred to the MICU, could not tolerate dialysis, her condition deteriorated and she died on January 6th, 1999.
- 30791-0304; 42 year old white male who was treated with pantoprazole 120 mg/d starting on June 3th, 1998 and ending on June 3th, 1999. Three years earlier, the patient had a diagnosis of ZES and pancreatic tumor with liver metastasis. On June 3th 1999, he presented at an ER with nausea, vomiting and diarrhea and was admitted with the diagnosis of gastroenteritis. On admission, he developed hematemesis and transferred to the ICU. Hematocrit was 32.4%. The patient was a Jehova's Witness and refused transfusion or Rx with blood products. An UGI endoscopy revealed an ulcer with a blood clot between the 2nd and 3rd portion of the duodenum. A CT scan revealed free air in the abdomen and an abscess extending to the retroperitoneum. On June 5th 1999, the patient was intubated and treated with antibiotics, levophed and dopamine. The hypotension led to renal failure and dialysis. His condition worsened, leading to a laparotomy. Medications included flagyl, lasix, ambien, thiamine, tylenol, and demerol. The patient died of continuing GI bleeding and sepsis on 6/20/99.
- 30791-0315; 39 year white female treated with pantoprazole 80 mg from 8/98 to 2/99. In November 1998, she was diagnosed as having metastatic gastrinoma of the liver. An UGI endoscopy revealed erosions in the lesser curvature of the stomach which resulted in blood loss and anemia. She was admitted to the hospital on February 17, 1999 for dehydration, low-grade fever and possible hepatic encephalopathy. She died 3 days later.
- 30791-0316; 43 year old white male who received 80 mg pantoprazole from 9/9/98 until 3/4/00. He had a history of ZES, diabetic neuropathy, and CVD. Was admitted to the hospital for treatment of infected lesions in hands and feet. He died on March 5, 2000. The cause of death was bronchopneumonia and sepsis of unknown duration.

7.2.2 Serious Adverse Events (SAEs)

There were 15 SAEs. In all but one patient (30791-0307) AEs were not considered by investigators to be related to pantoprazole treatment. In patient 0307, the SAE included nausea, lethargy and vertigo. Most of the events occurred with pantoprazole 40 mg bid.

- The list of SAEs in Study 307-US, W-AR Table 10.2.3A, Pages 70-71, is included as Appendix 2 of this review.

7.2.3. Optic Events

Four patients had visual abnormalities during the study period; three were considered by investigators possibly related to experimental drug treatment. The following are brief narratives of these three patients:

Patient 30791-0302; 39 y old woman with a history of chronic diarrhea, heartburn, sinus bradycardia, spondylosis, gastritis, duodenitis, and occasional headaches. She had blurred vision and eye floaters starting app. on 1/1/99 (study day 241). The eye floaters disappeared but the blurred vision persisted.

Patient 30791-0312; 65 y old woman with a history of borderline hypertension, arthritis, reported blurred vision on 8/1/99 (study day 383). The blurred vision disappeared without treatment on 11/22/99.

Patient 30791-0306; 41 year old man with diabetes and diabetic neuropathy, chronic pancreatitis, conjunctivitis, reported worsening of preexisting blurred vision on 8/30/99 (study day 356).

7.2.4 Safety-Related Discontinuations.

Seven patients were discontinued because of AEs. There were no differences between pantoprazole doses in the proportion of discontinuations due to AEs.

7.2.5 Treatment Emergent Adverse Events (TEAE).

At least 1 TEAE was reported for all but 2 patients at the data cutoff date. The most common TEAEs across treatment regimens were headache, diarrhea, nausea, abdominal pain, and back pain. The sponsor reports that there were significant differences among dosage regimens in the incidence of TEAEs for abdominal pain, asthenia, chest pain, constipation, edema, fever, hypokalemia, nausea, and vomiting. For purposes of thoroughness, the GI TEAEs displayed in W-AR Table 10.1.A, are included in this review as Appendix 3.

GI TEAEs Observed in Pivotal Study 307-US are included as Appendix 3.

7.2.6 Serum Gastrin

The sponsor reported that "there were no significant changes from baseline in mean gastrin levels at any time point during treatment for any dosage regimens".

7.3 Safety Data from Byk Gulden FK3038.

7.3.1 Deaths.

Two patients died during the study:

Patient #1 was a 56 year old South African Black male with a diagnosis of ZES and MEN-1 since 1991. During that year he underwent an exploratory laparotomy that resulted in resection of a duodenal wall gastrinoma. He also had a parathyroidectomy. He entered the study with a BAO of 97.8 mmil/h and required escalating doses of oral pantoprazole up to the maximum allotted of 160 mg per day. On March 1997, the patient underwent further surgery with removal of a gastrinoma and insulinoma. Pantoprazole was discontinued prior to surgery. Post-op, he was diagnosed with a perforated duodenal ulcer. He died on April 25, 1997 as a consequence of hemorrhage and septicemia.

Patient #504 was a 68 year old white female with a diagnosis of ZES since 1994. Before entry and during treatment phase, the serum gastrin level was 1000 ng/ml. For the first 6 months, she received 80 mg/d pantoprazole. The pantoprazole dose was eventually increased to 120 mg/d. Before the scheduled 10th study visit, she developed nausea, delayed gastric emptying and severe vomiting. The patient died February 14, 1997, after refusing food and medication.

7.3.2 Adverse Events

The report, (just a paragraph long) states that there were 9 SAEs in 4 patients. Except of vomiting, described in the mentioned patient #504, all the events were considered unrelated to study medication. Overall, a total of common 73 AEs were reported in the 11 enrolled patients. The most frequent reported common AEs were headache, diarrhea, dizziness, flu syndrome and rash. According to the investigators assessments, all the events were not or unlikely related to the pantoprazole therapy.

7.3.3 Gastric Histology

Five patients (#5, #6, #3, #7, #8) with no evidence of ECL-cell hyperplasia in the gastric histology at baseline, *developed* ECL-cell hyperplasia during the course of the study. Byk Gulden reports that an additional patient (#10) was diagnosed, during the study, to have "*ECL-cell-dysplasia*".

7.3.4 Reviewer Comments.

The cause for gastric ECL-cell hyperplasia in five patients during the pantoprazole maintenance treatment is of interest, but unclear whether related to the PPI, as all of these ZES patients had high serum gastrin (a stimulus for ECL-hyperplasia) prior to the experimental pantoprazole treatment. The same comment applies to the finding of gastric dysplasia in one of the treated patients.

8.0 Conclusions on Efficacy and Safety.

- Pivotal study W-AR Study 307 and supportive Byk Gulden study FK3038 showed that treatment with oral pantoprazole tablets decreases the gastric BAO of ZES patients and patients with idiopathic hypersecretory conditions either <5 mEq/h or <10 mEq/h. However, there were clear differences between degree in primary efficacy achieved in the 307-US trial and the FK3038 Byk Gulden trial. These differences in efficacy between the W-AR and Byk Gulden studies were specifically evident in the time required for the oral pantoprazole to control BAOs (longer in Byk Gulden patients), and, in the pantoprazole doses needed to achieve BAO control (higher in the Byk Gulden study). The reasons for this marked temporal and pantoprazole dose differences in achieving BAO control between the South African and USA ZES population are unclear. A possible but unproven explanation is that the different responses to pantoprazole in the Byk Gulden FK3038 study were related to the high proportion of South African Blacks enrolled in that study. In a recent large published review of 235 cases from the National Institutes of Health (NIH), Digestive Disease Branch, only 18% of the diagnosed ZES population were American Blacks (*Roy PK et al. Gastric Secretion in Zollinger-Ellison Syndrome. Correlation with clinical expression, tumor extent and role in diagnosis- a prospective NIH study of 235 patients and a review of 984 cases in the literature. Medicine, 80:189-222, 2001*).
- Overall, there were no unusual safety events reported from the W-AR and Byk Gulden study that would raise concern on the use of oral pantoprazole tablets in pathological hypersecretory states and ZES. The 7 deaths were related to complications of the underlying neoplasias. The *development* of gastric ECL-cell hyperplasia in 5 ZES patients, and a development of a gastric dysplasia in another patient treated for months with high, > 40 mg/d of oral maintenance pantoprazole doses needs to be noted. The latent concern is the transformation of ECL-cell hyperplasia into carcinoids. All PPIs, including pantoprazole, induce gastric ECL-hyperplasia and gastric carcinoids in experimental rodents. The underlying pathogenesis for the ECL-cell hyperplasia→carcinoid induced by PPIs, appears to be stimulation of gastrin production by the achlorhydric stomach. Byk Gulden, however, reported no changes in the serum gastrin levels (already high in ZES) during the course of the pantoprazole treatment. In its discussion, Byk Gulden points out that gastric carcinoids are not common in patients with ZES, unless the ZES is part of a MEN-1 syndrome. Of interest, there was only 1 MEN case in the Byk Gulden study, and this patient did not develop ECL-cell hyperplasia. *Unfortunately, upper GI endoscopy was not mandatory in the larger American 307-US study.* Because of the concerns the development of ECL-cell hyperplasia raised in the By Gulden study, and, the expressed concern with the experimental pantoprazole carcinogenesis, which included gastric cancers, long term maintenance use with oral pantoprazole requires a precise diagnosis and close surveillance of treated patients.

9.0 Proposed Label

The label proposed by the sponsor in the amended NDA 20987/SEI-007-BL submission of March 5, 2002 is acceptable.

10.0 Recommendations for Regulatory Actions

Based on my review of the submitted efficacy and safety data, I recommend the following:

1. To approve the use of oral pantoprazole tablets (PROTONIX[®]) for the proposed treatment of *Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome*.
2. To accept the proposed amended label submitted in the Amendment dated March 4, 2002.
3. To emphasize compliance with the agreed W-AR development plan for Phase IV *Long-Term Prospective Observational Study on the Incidence of Cancer Among Pantoprazole Users Compared to an Appropriate Control Group*.

APPENDIX 1

**307-US. Narrative of Patients with Needed Special Drug Adjustment for BAO
Control**

TABLE 1.5.2A. PATIENTS WITH SERIOUS AEs REPORTED AS SPONTANEOUS POSTMARKETING REPORTS:
12 JUN 2000 TO 31 DEC 2000

W-AR Control Number	Adverse Event Detail Term ^a	Date Report Received by Wyeth Ayerst	Country ^b	Age (y)	Sex	Daily Dose (mg)	Therapy Duration	Outcomes/ Actions ^c
HQ0331328AUG2000	Erythema multiforme, maculopapular rash, pyrexia	28 Aug 2000		71	F	20 mg/NR	NA	H, R
HQ0331528AUG2000	Skin vasculitis (NOS)	28 Aug 2000		81	F	NR	15 days	H
HQ0406929AUG2000	Drug interaction (NOS), hemorrhagic stroke, vomiting, ataxia, nausea, edema, ecchymosis, rib fracture, coma, international normalized ratio increased, fall, skull fracture, clavicle fracture	28 Aug 2000 14 Dec 2000		79	F	80 mg/day	11 days	H, D
HQ0475430AUG2000	Pancreatic carcinoma, hematemesis, melena, drug ineffective	30 Aug 2000		NR	M	40 mg/day	NR	NR
HQ0690506SEP2000	Anaphylactic shock, urticaria (NOS)	06 Sep 2000		41	F	40 mg/day	6 days	H, L, R
HQ0943507FEB2000	Cardiac failure aggravated	06 Dec 2000		89	M	40 mg BID	1 week	D
HQ0994614SEP2000	Glossitis, mouth ulceration, dysarthria	16 Sep 2000		44	M	20 mg/day	NR	NR
HQ0996214SEP2000	Sepsis (NOS), stomatitis, diarrhea (NOS), neutropenia, pseudomembranous colitis	14 Sep 2000		NR	M	NR	NR	D
HQ1370625SEP2000	Mood swings	22 Sep 2000		94	M	40 mg/day	10 days	R
HQ1384125SEP2000	Hemoglobin decreased, blood sodium decreased, hypotension (NOS)	16 Nov 2000		79	M	40 mg/day	NR	H, R
HQ1538628SEP2000	Pancreatitis (NOS)	11 Dec 2000		51	F	40 mg/day	NR	H
HQ1594929SEP2000	Thrombocytopenia, petechiae	28 Jul 2000		72	F	NR	NR	R

TABLE 1.5.2A. PATIENTS WITH SERIOUS AEs REPORTED AS SPONTANEOUS POSTMARKETING REPORTS:
12 JUN 2000 TO 31 DEC 2000

W-AR Control Number	Adverse Event Detail Term ^a	Date Report Received by Wyeth Averst	Country ^b	Age (y)	Sex	Daily Dose (mg)	Therapy Duration	Outcomes/ Actions ^c
HQ1615929SEP2000	Nonaccidental overdose, abnormal hepatic function (NOS)	29 Sep 2000		50	M	10 x 40 mg (overdose)	1 dose	H
HQ1932109OCT2000	Macular degeneration, hypermetropia, astigmatism, presbyopia	16 Nov 2000		66	F	40 mg/day	NR	S
HQ2264116OCT2000	Hepatitis fulminant, hepatic failure, hepatitis B	23 Oct 2000		86	F	40 mg every other day	NR	H, D
HQ2294116OCT2000	Dysmenorrhea, intermenstrual bleeding	13 Oct 2000		NR	F	40 mg/day	20 months	NR
HQ2421318OCT2000	Vasovagal attack, upper abdominal pain	20 Nov 2000		67	F	40 mg/day	1 day	H, R
HQ2490219OCT2000	Premature delivery of infant, complications of maternal exposure to therapeutic drugs	19 Oct 2000		NR	F	20 mg/day	31 days	NR
HQ2531120OCT2000	Cellulitis	20 Oct 2000		54	M	40 mg/day	4 days	H, R
HQ2678124OCT2000	Pain in limb, arthralgia	06 Nov 2000		63	M	20 mg/day	304 days	R
HQ2678224OCT2000	Hemolytic anemia (NOS)	24 Oct 2000		69	F	NR	189	H, R
HQ2678424OCT2000	Anaphylactic reaction	24 Oct 2000		49	M	20 mg	1 dose	NR
HQ2806626OCT2000	Hepatic function abnormal (NOS)	26 Oct 2000		NR	M	40 mg/NR	NR	H
HQ2836227OCT2000	Jaundice (NOS), dizziness, hepatic function abnormal (NOS), AST and ALT increased	27 Dec 2000		51	F	40 mg/day	70 days	H
HQ2844227OCT2000	Interstitial nephritis, granuloma (NOS)	27 Oct 2000		51	M	40 mg/day	33 days	H
HQ2844827OCT2000	Depression (NEC)	27 Oct 2000		43	M	NR	14 days	NR
HQ2996431OCT2000	Anaphylactic reaction	31 Oct 2000		35	F	NR	NR	L, R
HQ3180114APR2000	Acute renal failure, interstitial nephritis, cholestatic hepatitis	30 Aug 2000		83	F	40 mg/day	80 days	H
HQ3510810NOV2000	Paraplegia	28 Nov 2000		NR	F	40 mg/day	NR	NR
HQ3941420NOV2000	Agitation	20 Nov 2000		75	F	40 mg/day	NR	H, R

TABLE 1.5.2A. PATIENTS WITH SERIOUS AEs REPORTED AS SPONTANEOUS POSTMARKETING REPORTS:
12 JUN 2000 TO 31 DEC 2000

W-AR Control Number	Adverse Event Detail Term ^a	Date Report Received by Wyeth Ayerst	Country ^b	Age (y)	Sex	Daily Dose (mg)	Therapy Duration	Outcomes/ Actions ^c
HQ4104427NOV2000	Pancreatic carcinoma	23 Nov 2000		NR	F	NA	NA	H
HQ4160328NOV2000	Agranulocytosis, stomatitis, increased erythrocyte sedimentation rate	28 Nov 2000		NR	F	40 mg/day	"about 1 month"	NR
HQ4196429NOV2000	Abdominal pain, upper	14 Dec 2000		65	F	40 mg/day	1 month	R
HQ4452605DEC2000	Visual disturbance (NOS), confusion	05 Dec 2000		60	F	40 mg/day	5 years	R
HQ4580207DEC2000	Vision blurred	07 Dec 2000		89	F	20 mg/day	7 days	S
HQ4656408DEC2000	Hepatocellular damage, abnormal hepatic function	08 Dec 2000		NR	M	20 mg/day reduced to dose unknown	NA	NR
HQ4711011DEC2000	Pyrexia, nausea, back pain, malaise, pallor, headache (NOS), sweating increased, dizziness, joint stiffness	11 Dec 2000		30	F	20 mg/day	7 days	H
HQ4818413DEC2000	Headache (NOS), alopecia	19 Dec 2000		50	F	40 mg/day	NR	S
HQ4908115DEC2000	Death (NOS)	15 Jan 2001		NR	NR	NR	NR	D
HQ4974218DEC2000	Myalgia; blood creatine phosphokinase increased	18 Dec 2000		34	M	40 mg/day	NR	H
HQ5152621DEC2000	Hypertension aggravated, palpitations	21 Dec 2000		64	F	40 mg/day	NR	NR
HQ5232522DEC2000	Thrombocytopenia	10 Jan 2001		NR	F	NR	NR	H, D
HQ5249127DEC2000	Bone marrow depression NOS; deafness NOS	22 Dec 2000		67	F	40 mg/day	8 days	H
HQ5290627DEC2000	Acute renal failure, interstitial nephritis	27 Dec 2000		67	M	40 mg/day	3 weeks	H, R

TABLE 1.5.2A. PATIENTS WITH SERIOUS AEs REPORTED AS SPONTANEOUS POSTMARKETING REPORTS:
12 JUN 2000 TO 31 DEC 2000

W-AR Control Number	Adverse Event Detail Term ^a	Date Report Received by Wyeth Ayerst	Country ^b	Age (y)	Sex	Daily Dose (mg)	Therapy Duration	Outcomes/ Actions ^c
HQ5374729DEC2000	Hypersensitivity NOS; oedema lower limb; eyelid edema; albuminuria present; hypoproteinemia; face edema; weight increased	29 Dec 2000		34	F	40 mg/day	29 days	L, H
HQ5500603JAN2001	Bone marrow depression, deafness (NOS)	12 Feb 2001		67	F	40 mg/day	8 days	H
HQ6585230JAN2001	Urticaria NOS; eyelid edema; throat tightness	20 Dec 2000		51	F	40 mg/day	NR	R
HQ7452416JUN2000	Hematuria present	09 Aug 2000		85	M	40 mg/day	NR	H
HQ7628221JUN2000	Coagulation time prolonged (NOS), drug interaction (NOS)	21 Jun 2000		46	F	40 mg/day	28 days	NR
HQ7637021JUN2000	Cholestasis	05 Dec 2000		71	M	20 mg BID	9 months	NR
HQ7637621JUN2000	Pancreatitis (NOS)	21 Jun 2000		63	M	40 mg/day	13 days	R
HQ7834326JUN2000	Gynecomastia	26 Jun 2000		38	M	20 to 40 mg/day	20 months	NR
HQ8098503JUL2000	Chest pain, diarrhea (NOS), peripheral edema	24 Aug 2000		74	F	40 mg/day	10 days	H
HQ8480113JUL2000	Thyroid nodule	21 Aug 2000		47	F	40 mg/day	NR	NR
HQ8592117JUL2000	Nonaccidental overdose, thinking abnormal, flight of ideas	10 Aug 2000		53	F	40 mg BID and 40 mg QID	5 weeks	R
HQ8616117JUL2000	Pancreatic carcinoma (NOS), jaundice - extrahepatic, obstructive (NOS)	22 Nov 2000		70	F	NR	16 days	H
HQ9092627JUL2000	Chest pain, sweating increased, dyspnoea, hallucinations (NOS), dizziness, syncope, drug interaction	21 Aug 2000		66	F	40 mg BID	NR	NR
HQ9094927JUL2000	Convulsions (NOS), muscle cramps, fall	21 Sep 2000		38	M	40 mg/NR	1 day	NR

TABLE 1.5.2A. PATIENTS WITH SERIOUS AEs REPORTED AS SPONTANEOUS POSTMARKETING REPORTS:
12 JUN 2000 TO 31 DEC 2000

W-AR Control Number	Adverse Event Detail Term ^a	Date Report Received by Wyeth Ayerst	Country ^b	Age (y)	Sex	Daily Dose (mg)	Therapy Duration	Outcomes/ Actions ^c
HQ9508307AUG2000	Arthralgia	07 Aug 2000		37	M	20 mg/day	27 days	NR
HQ9508407AUG2000	Prothrombin time prolonged, drug interaction (NOS)	07 Aug 2000		58	F	40 mg/day	19 days	L, R
HQ9508607AUG2000	Jaundice (NOS), increases in alkaline phosphatase, bilirubin, aspartate aminotransferase, gamma-glutamyltransferase, eosinophilia, and cholecystitis (NOS)	16 Nov 2000		43	M	40 mg/day	13 days	NR
HQ9622609AUG2000	Sedation	27 Oct 2000		42	F	40 mg/day	3 days	R
HQ9644309AUG2000	Depression aggravated	09 Aug 2000		70	F	40 mg/day	11 days	H
HQ9756611AUG2000	Accidental overdose	09 Aug 2000		29	M	8 to 10 tablets month	1 dose	H, R
HQ9758711AUG2000	Grand mal convulsions, mania	25 Sep 2000		74	M	NR	NR	H, R
HQ9786614AUG2000	Cholestatic hepatitis	14 Aug 2000		76	F	40 mg BID	NA	NR

a: Adverse event (AE) term: AEs are listed by World Health Organization Adverse Reaction Terms (WHO-ART)

b: Countries: AS = Australia; BE = Belgium; CA = Canada; FR = France; GE = Germany; IT = Italy; NE = Netherlands; SW = Switzerland; UK = United Kingdom; US = United States.

c: Outcomes/actions: D = died; H = hospitalized; L = life threatening; R = recovered; S = disabled.

Abbreviations: BID = twice daily; NEC = not elsewhere classified; NOS = not otherwise specified; NR = not reported; NA = Not available.

APPENDIX 2

307-US. List of SAEs

9.2.3.1 Individual Control of Acid Output

Nine (9) patients had average AO rates during treatment with pantoprazole that exceeded the criteria for control of AO.

Patient 30789-0303, a 47-year-old man with sporadic ZES who had undergone acid-reducing surgery (vagotomy), had AO rates at various evaluations that exceeded 5 mEq/h. The average AO rates were 5.4 mEq/h on day 2, 6.9 mEq/h on day 28, 9.0 mEq/h at month 3, and 8.9 mEq/h at month 6. The average AO rates were less than 5 mEq/h from months 9 through 18. At months 21 and 24, the average AO rates were 5.5 mEq/h and 6.3 mEq/h, respectively. The patient received 40 mg BID throughout the study. The dose was not increased at the discretion of the investigator.

Patient 30789-0304, a 50-year-old man who had ZES with MEN-1, had an average AO rate of 10.9 mEq/h at month 9 (study day 267). The patient began pantoprazole treatment with 40 mg BID. The dosage was increased to 80 mg BID to improve response. At an evaluation 2 weeks later (study day 281), the average AO rate was 1.8 mEq/h. The AO rate remained below 10 mEq/h during month 12. At the initial evaluation during month 15 (study day 454), the average AO rate was 26.8 mEq/h. The dosage was increased to 120 mg BID. At an evaluation 2 weeks later (study day 468), the average AO rate was 0.1 mEq/h. The patient continued to take 120 mg BID and AO rates remained suppressed through month 21.

Patient 30790-0304, a 32-year-old woman who had ZES with MEN-1, had an average AO rate of 27.1 mEq/h at month 18 (day 549) while receiving 40 mg BID. Eighteen (18) days later (study day 567), the average AO rate was 6.9 mEq/h. The patient had started treatment with 40 mg BID and received an increase in dosage to improve response on day 5. The dosage was increased to 80 mg BID and average AO measurements were less than 5 mEq/h through study day 260. The dosage was decreased to 40 mg BID on study day 260. The patient missed taking tablets on many occasions throughout the study (see section 9.2.3.3, Discussion of Patients Whose Dose Was Adjusted).

Patient 30790-0305, a 30-year-old woman who had sporadic ZES, began pantoprazole treatment with 80 mg BID. At month 3 (study days 85 and 86), the average AO rate increased from less than 5 mEq/h to 32.7 mEq/h. The dosage was increased to 120 mg BID. Approximately 3 weeks later (study day 115), the average AO rate was 4.6 mEq/h. AO

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rates remained less than 10 mEq/h through month 24 (see section 9.2.3.2, Discussion of Patients Who Received Pantoprazole 240 mg daily).

Patient 30791-0303, a 51-year-old man who had sporadic ZES, had AO measurements averaging 10.5 mEq/h at the month-6 visit (day 183). The dosage was not adjusted at this time but subsequent average AO rates through month 27 were less than 10 mEq/h (see section 9.2.3.3, Discussion of Patients Whose Dose Was Adjusted).

Patient 30791-0306, a 59-year-old man with ZES who had had gastric acid-reducing surgery (Billroth procedure), had an AO rate of 6.4 mEq/h on day 190. The dosage was increased to 80 mg BID from 40 mg BID to improve response. Thereafter, the AO rates were generally less than 5 mEq/h. On day 147, treatment was stopped because of mild dizziness and paresthesia considered by the investigator to be unrelated to treatment with pantoprazole; the symptoms continued, but treatment was reintroduced 19 days later.

Patient 30791-0312, a 65-year-old woman who had had acid-reducing surgery (Whipple procedure), had AO measurements that averaged 5.8 mEq/h at month 9 and 7.4 mEq/h at month 16. Her dosage was increased from 40 mg BID to 80 mg BID at month 18 and subsequent AO rates were less than 5 mEq/h.

Patient 30791-0314, a 59-year-old woman who had ZES with MEN-1, had an average AO rate of 39.9 mEq/h at month 3. The patient was taking 40 mg BID but missed taking tablets for 1 day on study day 94. The patient took 80 mg BID for 2 days and AO levels fell to less than 10 mEq/h. The dosage was decreased to 40 mg BID and AO levels remained below 10 mEq/h, despite occasional non-compliance.

Patient 30791-0316, a 41-year-old man who had sporadic ZES, had an average AO rate of 16.8 mEq/h at month 9. The dosage of pantoprazole was increased from 40 mg BID to 80 mg BID. Subsequently, the average AO rate fell below 10 mEq/h and remained suppressed through month 15.

9.2.3.2 Discussion of Patients Who Received Pantoprazole 240 mg Daily

Most patients received pantoprazole regimens of 40 mg BID or 80 mg BID to control AO levels. Four (4) patients received regimens of 120 mg BID and 1 patient received a regimen of 80 mg TID. Of these 5 patients, 4 had increases in dose to improve response and 1

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(30799-0302) began treatment with 120 mg BID and had the dosage reduced to 80 mg BID because of adverse events.

Patient 30789-0304, a 50-year-old man who had ZES with MEN-1, began pantoprazole treatment with 40 mg BID. At months 9 and 15, the dosage was increased to 80 mg BID and 120 mg BID, respectively, to improve response (see section 9.2.3.1, Individual Control of Acid Output).

Patient 30790-0302, a 42-year-old woman with idiopathic hypersecretory disease, began pantoprazole treatment with 80 mg BID. On study day 162, the AO rate at the initial 15-minute collection was 13.7 mEq/h (average AO rate, 6.4 mEq/h). The dosage was increased to 80 mg TID on day 166 to improve response. Thereafter, AO rates remained below 10 mEq/h under the same dosage regimen.

Patient 30790-0305, a 30-year-old woman who had sporadic ZES, began pantoprazole treatment with 80 mg BID. At month 3 (study days 85 and 86), the average AO rate increased from less than 5 mEq/h to 32.7 mEq/h. The dosage was increased to 120 mg BID to improve response. Thereafter, AO rates were less than 10 mEq/h. The patient was non-compliant at various times throughout the study. The patient remained in the study.

Patient 30791-0304, a 41-year-old man with ZES, began pantoprazole treatment with 80 mg BID. The dosage was increased to 120 mg BID on study day 56 (~ month 2) at the discretion of the investigator to improve response, although AO rates were less than 5 mEq/h. At month 6 (study day 222), the patient's AO rate increased to 13.9 mEq/h at the first 15-minute evaluation. However, AO rates fell below 5 mEq/h on subsequent measurements the same day and remained suppressed throughout the study. On 30 Jun 1999 (~ month 11), the patient died because of a GI hemorrhage unrelated to treatment with pantoprazole (see section 10.2.1, Deaths).

Patient 30799-0302, a 67-year-old man with ZES, began pantoprazole treatment with 120 mg BID. The dosage was reduced to 80 mg BID at approximately study day 11 because of nausea, tinnitus, kidney pain, and urinary frequency. All of these adverse events except tinnitus disappeared. The AO rates were less than 5 mEq/h throughout treatment.

APPENDIX 3

Study 307-US. GI TEAES

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TABLE 10.1.IA. SUMMARY OF TEAES BY DOSAGE REGIMEN: NUMBER (%) OF PATIENTS

Body System ^a Adverse Event	Pantoprazole			Total (n = 35)	Fisher's Exact p-value ^b
	40 mg BID (n = 25)	80 mg BID (n = 8)	120 mg BID (n = 2)		
Any adverse event	23 (92)	8 (100)	2 (100)	33 (94)	1
Body as a Whole					
Abdomen enlarged	1 (4)	0	0	1 (3)	1
Abdominal pain	5 (20)	5 (63)	1 (50)	11 (31)	0.046*
Accidental injury	3 (12)	0	1 (50)	4 (11)	0.155
Adenoma	1 (4)	0	0	1 (3)	1
Asthenia	0	2 (25)	1 (50)	3 (9)	0.022*
Back pain	8 (32)	2 (25)	1 (50)	11 (31)	1
Carcinoma	0	1 (13)	0	1 (3)	0.286
Chest pain	0	2 (25)	1 (50)	3 (9)	0.022*
Chest pain substernal	0	0	1 (50)	1 (3)	0.057
Cyst	1 (4)	0	0	1 (3)	1
Drug abuse	1 (4)	0	0	1 (3)	1
Fever	0	1 (13)	2 (100)	3 (9)	0.001**
Flu syndrome	3 (12)	0	0	3 (9)	0.633
Generalized edema	2 (8)	0	1 (50)	3 (9)	0.175
Headache	12 (48)	3 (38)	1 (50)	16 (46)	0.846
Infection	3 (12)	2 (25)	0	5 (14)	0.688
Lab test abnormal	0	1 (13)	0	1 (3)	0.286
Neck pain	0	1 (13)	0	1 (3)	0.286
Neck rigidity	1 (4)	1 (13)	0	2 (6)	0.496
Neoplasm	1 (4)	0	0	1 (3)	1
Pain	6 (24)	1 (13)	1 (50)	8 (23)	0.373
Sepsis	3 (12)	0	1 (50)	4 (11)	0.155
Cardiovascular System					
Arrhythmia	0	0	1 (50)	1 (3)	0.057
Arterial anomaly	1 (4)	0	0	1 (3)	1
Cardiovascular physical finding	1 (4)	0	0	1 (3)	1
Congestive heart failure	1 (4)	0	1 (50)	2 (6)	0.16

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TABLE 10.1.1A. SUMMARY OF TEAES BY DOSAGE REGIMEN: NUMBER (%) OF PATIENTS

Body System ^a Adverse Event	Pantoprazole			Total (n = 35)	Fisher's Exact p-value ^b
	40 mg BID (n = 25)	80 mg BID (n = 8)	120 mg BID (n = 2)		
Cardiovascular System (cont'd)					
Coronary artery disorder	0	1 (13)	0	1 (3)	0.286
Heart arrest	1 (4)	1 (13)	1 (50)	3 (9)	0.083
Heart failure	1 (4)	0	0	1 (3)	1
Hemorrhage	1 (4)	0	0	1 (3)	1
Hypertension	3 (12)	0	0	3 (9)	0.633
Hypotension	0	0	1 (50)	1 (3)	0.057
Migraine	0	1 (13)	0	1 (3)	0.286
Palpitation	0	0	1 (50)	1 (3)	0.057
Pulmonary embolus	0	0	1 (50)	1 (3)	0.057
Shock	0	0	1 (50)	1 (3)	0.057
Tachycardia	1 (4)	0	1 (50)	2 (6)	0.16
Vasodilatation	0	1 (13)	0	1 (3)	0.286
Digestive System					
Anorexia	1 (4)	0	1 (50)	2 (6)	0.16
Cholecystitis	1 (4)	0	1 (50)	2 (6)	0.16
Constipation	2 (8)	3 (38)	2 (100)	7 (20)	0.006**
Diarrhea	7 (28)	4 (50)	1 (50)	12 (34)	0.38
Dry mouth	1 (4)	0	0	1 (3)	1
Dyspepsia	8 (32)	0	0	8 (23)	0.192
Eruclation	1 (4)	0	0	1 (3)	1
Esophagitis	0	1 (13)	0	1 (3)	0.286
Gastroenteritis	0	1 (13)	0	1 (3)	0.286
GI hemorrhage	0	0	1 (50)	1 (3)	0.057
Glossitis	0	1 (13)	0	1 (3)	0.286
Increased appetite	0	1 (13)	0	1 (3)	0.286
Intestinal obstruction	1 (4)	0	0	1 (3)	1
Liver fatty deposit	1 (4)	0	0	1 (3)	1
Liver function tests abnormal	1 (4)	0	0	1 (3)	1
Melena	1 (4)	0	0	1 (3)	1

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4/2/02 06:58:49 PM
MEDICAL OFFICER

MTL agrees with the recomm. : a) to approve
oral PROTONIX for Tx of Z-E; b) accept
the sponsor's proposed revised labeling; and c) emphasize
compliance with the Clin Plan for Phase IV
L-T cancer incidence study.