12. Reviewer's Additional Comments

This single center, single investigator study in apparently healthy volunteers [Protocol 3001K1-100-US (GMR-32020)] was the second of the two critical clinical trials in NDA 20-988. Results of this study were submitted by the sponsor as supportive of those from pivotal trial 3001K1-309-US. The main approach consisted of a clinical pharmacology model using a PD measure of response to four doses PANTO I.V. over a six-fold range (20, 40, 80 and 120 mg) in order to assess the ability of increasing doses of the drug to inhibit pentagastrin-stimulated acid output (PSAO). The results of these evaluations are expected to serve as a model for patients with Zollinger-Ellison syndrome (Z-ES). Using this PD model, doses of PANTO I.V. from 20 to 120 mg were compared with each other to determine the PD response. Comparison was also made with PANTO tablet, famotidine (FAM) I.V. and placebo (PL) I.V. This is a rigorous model because the gastric acid secretion stimulant pentagastrin (PG) was administered for 24 to 25 hours, beginning 1h before (or at the same time as in the case of PANTO tablet) administration of single doses of PANTO or comparator, and continued for 24h after the single dose.

The study was well-designed and apparently well executed. However, before we go any further, it is important to address an initial, essential, question: **how applicable to the GERD situation are results of PD studies in healthy subjects?** The evidence at hand suggests that there is no reason to suspect that GERD patients may respond differently from the acid secretion viewpoint than healthy volunteers; most patients with only GERD are **neither potential nor real hypersecretors**. This issue was addressed by B. Hirschowitz in the early 1990s [Gastroenterology 98:A60 (1990); later published as a full paper[27] in the same journal]. This investigator, one of the top in this field, studied fasting gastric contents (volume, pH, H^+, pepsin, and bile) and basal and PG-stimulated H^+ and pepsin in 696 patients, 169 with endoscopically defined (and graded 1 to 4) erosive esophagitis (EE) and 527 controls without esophagitis. It was shown that esophagitis (and its complication-stricture) were not related to high acid and pepsin secretion. Dr. Hirschowitz's results further demonstrated that, unless they have a concomitant duodenal ulcer (DU), GERD patients do not secrete acid to the same extent as DU patients (not the subject of NDA 20-987 or 20-988). Moreover, according to this publication, when properly classified and matched for background (gender and the presence of DU), even patients with Barrett's esophagus did not seem to have greater outputs of gastric acid or pepsin than esophagitis patients without Barrett's.[28]

This important background information is now considered together with the data from NDA 20-987. These demonstrated that at the oral dose of 40 mg per day – PANTO is effective in the healing of lesions and improvement of symptoms of erosive esophagitis. It follows that PD data in healthy volunteers are adequate subrogates for demonstrating antisecretory effects of PANTO in GERD. The conclusion that an essential question has been answered in that PK-PD data from healthy volunteers are entirely relevant to the GERD population, facilitates addressing of the key matter which is to identify an intravenous dose (and dose regimen) that would attain the same degree of antisecretory effect as the established oral regimen of 40 mg per day. This was clearly

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[27] "A Critical Analysis, With Appropriate Controls, of Gastric Acid and Pepsin Secretion in Esophagitis"

[28] M.J. Collen et al. [Gastroenterology 98:654-661 (1990)] described a subgroup of patients with long-standing symptomatic GERD who were hypersecretors and required increased acid-suppressive therapy. Many of these individuals also had underlying Barrett's epithelium.

shown in study –309-US. What follows below is a summary assessment of whether the results of study –100-US support the PD equivalence of intravenous administration of PANTO 40 mg to the recommended oral dose of 40 mg once-a-day.

An additional reason to test 40 mg I.V. is that 40 mg once-a-day is the current dose for most indications in the over 50 countries where the oral drug is marketed by Byk Gulden. Inclusion of the 20-mg I.V. dose was important to assess a dose response [in study –309-US, this dose of PANTO produced significantly less inhibition of gastric acid secretion than the 40 mg dose and this finding needs to be confirmed]. The 80- and 120-mg doses are not needed in GERD patients but it is important to test these doses because of the difficulty of controlling gastric acid secretion in Z-ES patients. Nonetheless, inclusion of these high doses are important to gain further data on the dose response. Inclusion of the 40-mg oral dose, famotidine 20-mg I.V. and a placebo group were important arms of the protocol. These treatment groups provided comparison to the recommended oral dose of PANTO, and comparison to the recommended therapeutic dose of famotidine [which has also been approved for use in hypersecretory pathological conditions). In addition, they provided a better understanding of PANTO pharmacodynamics.

Although pentagastrin (PG) is a commonly used gastric secretion stimulant under nearly standardized conditions, it is worth mentioning its limitations when used as a model of hypersecretory conditions such as Z-ES. Studies in healthy subjects have shown that 80% maximal gastric secretory response is reached in ca. 80% of individuals with a dose of 0.6 μg/Kg/h. But this dose of PG is not enough for a model to be used instead of Z-ES patients because **the latter are known hypersecretors.** Maximal gastric secretion in nearly all experimental subjects in whom the gastric acid secretion machinery is normal, is observed at PG doses of 6 μg/Kg/h (a 10-fold higher dose of the stimulant), but, as shown in study –300-US, at these higher doses of PG the incidence of side effects is high. In study –100-US, the sponsor elected a PG dose of 1 μg/Kg/h. Their rationale was that, according to several publications, this PG is tolerable and produces a near maximal acid secretion that is sustainable for 24h in healthy subjects and comparable to the lower range of AO seen in patients with Z-ES. The reviewer concludes that the experimental conditions in study –100-US **are applicable to the GERD patient**.

In study –100-US the PD response was evaluated using three adequate parameters that were calculated using 10 mEq/h as the cut-off point. These consisted of onset time, duration and magnitude of response. In the Clinical Report, the effects seen with 80 and 120 PANTO I.V. are emphasized. This information is applicable to the Z-ES indication. But this is not the subject of the current review. In the present review, emphasis is put on results obtained with 40 mg PANTO i.V. in comparison with orally administered PANTO at 40 mg once-a-day.

- Refer to Table 19. In study –100-US, acid suppression activity was observed 0.25 to 4.5h (mean-1.6h) after administration of the 40 mg I.V. dose; this time of onset was shorter than the 6 to 16.5h (mean-10.3h) seen with 40 mg orally administered dose. The 20 mg PANTO I.V. (mean onset=2.8h) was less effective than the 40 mg PANTO I.V.

- 40 mg PANTO I.V. provided a mean of 15.9h (range=2.5 to 23.5h) duration of gastric secretion activity and this was longer than the 5.0h (range-1.5 to 8h) seen with the 40 mg

PANTO oral dose. The 20 mg PANTO I.V. (mean duration=8.4h, range=0 to 22.3h) was less effective than the 40 mg PANTO I.V.

- 40 mg PANTO I.V. (mean=181 mEq) drastically reduced cumulative AO compared with PL (mean=829 mEq). The mean cumulative AO observed with 40 mg PANTO oral was 294 mEq; with 20 mg PANTO, it was 355 mEq.

- Acid suppression activity was observed within 15 to 30 min. and lasted a mean of 21h after I.V. administration of higher doses of the drug (80 and 120 mg I.V.); acid output was decreased to less than 10 mEq/h within 1h of these high doses, to values (80 and 64 mEq, respectively) that were lower than those seen with any treatment group. As already noted, inclusion of these high doses of PANTO I.V. was useful to demonstrate a drug response in the PD parameters evaluated.

- In addition, as pointed out by the sponsor, there was no tolerance to the gastric acid stimulating effects of PG following continuous infusion for 24h in apparently healthy subjects in this gastric acid hypersecretion model.

- The data depicted in Table 20 (hourly rate of acid output in mEq/h) demonstrate that for both the entire 24-h study period and for each of the sequenntial 6-h periods (especially the first two), 40 mg PANTO I.V. gave lower rates of acid output than the 40 mg PANTO oral.

- From all the information in study –100-US, it is concluded that 40 mg PANTO I.V. is as effective as the 40 mg oral dose of the drug.

In study –100-US, 40 (and up to 120) mg doses of intravenously administered PANTO were safe and well-tolerated. Neither deaths nor serious events were reported. AEs leading to discontinuation [n=6] included mostly mild dyspepsia and gastrointestinal hemorrhage due to treatment methodology (NG tube placement). All AEs resolved wtihout clinical sequelae. There were no reports of clinically important changes in laboratory results.

XII. OVERALL COMMENTS/CONCLUSIONS ON EFFICACY

The sponsor of NDA 20-987 submitted pharmacodynamic (PD) data from two pivotal studies, -300-US in GERD patients and –100-US in healthy volunteers in support of intravenous pantoprazole. Approval is requested for the marketing of 40 mg PANTO intravenous formulation as an alternative to oral dosage (40 mg) for short-term use in GERD patients unable to take the oral medication. This is a rather restricted indication since it includes only GERD patients (no other indication) that have already started on or are being treated with 40 mg of the oral formulation of the drug. The latter was found to be safe and effective and therefore recommended for approval for the treatment and relief of symptoms associated with erosive esophagitis (MOR of April 9, 1999, Dr. Hugo E. Gallo-Torres). With these considerations in mind, the intravenous dose of 40 mg PANTO should demonstrate the same [equipotent/equivalent] antisecretory effects as the 40 mg oral PANTO formulation. From his review of the evidence, in Clinical Reports –09-US and –100-US, the reviewer concludes that

the 40 mg I.V. once-a-day dose of the drug can maintain the same degree of antisecretory activity already obtained after a 7-day regimen of 40 mg PO. This conclusion is further supported by results from many other comparisons or considerations. The absolute bioavailability of PANTO from an oral tablet formulation was 0.77 (Study 7E/91). In a gastric fistula dog model, at I.V. doses of 0.95, 1.9 and 3.8 mg/Kg PANTO rapidly caused increases of at least 1 pH unit (>90% inhibition of acid secretion); these results were very similar to those seen when, in other studies, the drug was administered orally. In the acute gastric fistula rat model, where gastric acid secretion was stimulated with the muscarinic receptor agonist bethanecol, PANTO administered I.V. was as potent as the drug administered orally [ED_{50} (mg/Kg), I.V.=0.5; PO=0.7]. Similar conclusions were arrived at when using the impromidine-induced gastric acid secretion in the Hedenhain pouch dog model [ED_{50} (mg/Kg), I.V.=0.17; PO=1.4]. Additionally, Phase II study A9918 in apparently healthy volunteers showed that following once daily administration, PANTO 40 mg I.V. was equipotent to PANTO mg PO in reducing 24-h intragastric acidity. Both formulations (40 mg PANTO I.V. and 40 mg enteric coated tablets) were shown to be equipotent in study FAPO47 where the parameters of PD assessment were % time pH <4, % time pH <3 and 24-h median pH.

In what follows, the reviewer provides answers to the questions proposed in Section IX of this review, pertinent to the approval of 40 mg I.V. PANTO.

The question of whether 40 mg I.V. PANTO once-a-day is effective is settled by results of studies –309-US and –100-US and further supported by data from Phase II studies A9918 and FHP047. Results of all these studies provide an answer to the question of whether an "adequate antisecretory activity can be maintained". As shown in Table 6, regardless of the study population analyzed (ITT, M-ITT or VFE) or the statistical method utilized (t test, sign test or signed-rank test), with 40 mg PANTO, $MAO_{LI.V.}$ was far lower (6.62 mEq/h in the ITT population) than PL (29.19 mEq/h). This marked superiority of the PANTO 40 mg I.V. dose to PL was confirmed in study –100-US.

The answer to the third question is YES. Studies in NDA 20-988 show that 40 mg I.V. PANTO once-a-day can be used as an alternate to 40 mg oral PANTO per day in those erosive esophagitis patients who are unable to take oral medication. From the detailed review of the data in critical study –309-US, the reviewer concludes that $MAO_{LI.V.} = MAO_{LPO}$ and $BAO_{LI.V.} = BAO_{LPO}$. The use of 40 mg PANTO I.V. as an alternate to 40 mg oral formulation of the drug is supported by results of pivotal study –100-US and Phase II trials A9918 and FHP047 where PD parameters of gastric acid secretion other than MAO and BAO were evaluated.

The answer to the fourth question is also YES since all studies, whether Phase III or II, have demonstrated that intravenously administered PANTO at the proposed doses (40 mg I.V. in all studies) or even higher (80 and 120 mg in study –100-US) is safe and well-tolerated.

The question of only "one critical clinical trial" (-309-US) used for approval is addressed next. The reviewer has presented reasonable arguments demonstrating that this is not a "one trial" situation. It is true that the most important study in NDA 20-988 is –309-US because, in this trial, the evaluations were done in the target population, the GERD patient. But the evaluation in this trial did not consist of responses in clinical endpoints (healing of esophageal lesions of

erosive esophagitis). Instead, as agreed during pre-NDA meeting of April 29, 1997 between FDA representatives and sponsor's representatives, inhibition of gastric acid secretion is an acceptable endpoint. In the reviewer's additional comments section of this review (XI.12), the rationale to consider results of healthy volunteers study –100-US as pivotal was given. In this study efficacy was assessed on the basis of PD parameters. It was concluded that one can extrapotate PD findings in healthy volunteers to patients with GERD, provided that the latter do not have a concomitant duodenal ulcer. This is because most patients are not considered hypersecretors.

Since an effect of the 40 mg PANTO I.V. has previously been demonstrated in Phase II (A9918 and FHP047), Phase III (-100-US) and even preclinical evaluations, study –309-US is no longer testing the hypotheses that an effect exists. Study –309-US is measuring the magnitude of the effect (the magnitude of the difference, if any, between 40 mg PANTO I.V. and 40 mg PANTO PO).

The answer to the sixth question is that approval of the 20 mg I.V. PANTO dose cannot be recommended. The results of study -309-US showed that whether using MAO or BAO as the PD parameters of comparison, the 20 mg PANTO I.V. was not consistently equivalent to the 40 mg PANTO PO. Similarly, in study –100-US, where the PD parameters of evaluation were other than MAO and BAO, the 20 mg PANTO I.V. was not as effective as the 40 mg PANTO I.V.

One final answer (to question 7) is that 40 mg PANTO I.V. cannot be recommended for use. Results of study –309-US showed that this dose of PANTO does not produce the same PD effect on the first day in comparison to the 40 mg PANTO PO ($MAO_{F.I.V.}$ vs MAO_{LPO} and $BAO_{FI.V.}$ vs BAO_{LPO}). Although PANTO 40 mg I.V. can be recommended as an alternate to those GERD patients who are already on PANTO 40 mg PO, this I.V. dosage form of the drug cannot be recommended in instances where the GERD patient may be needed to be treated parenterally from the start. The two studies submitted by the suponsor in support of the expansion of the requested indication, BAT010 and FK3050, did not use useful designs (Table 2 of the current review). Results of these inadequate studies were not reviewed here.

XIII. OVERALL COMMENTS/CONCLUSIONS ON SAFETY

Information from all clinical trials and additional data in NDA 20-988 suggests that at doses of 40 mg once-a-day (and up to 120 mg per day), intravenously administered PANTO is safe and well-tolerated. Further considerations to overall safety are addressed in the review of the SU.

XIV. RECOMMENDATIONS FOR REGULATORY ACTION

1. Approval of intravenous PANTO (40 mg once-a-day) as an alternate to oral dosage (40 mg per day) is recommended. This recommendation is based on the review of the evidence from clinical data in NDA 20-988. These data consisted of PD/PK evaluations in the GERD population in study –309-US and in apparently healthy volunteers in study –100-US.

2. The conditions of usage should better be specified in a labeling separate from that for the oral PANTO. The labeling for I.V. PANTO should incorporate all pertinent information already in the proposed labeling for oral PANTO.

3. Intravenous PANTO should be used only in that indication for which oral PANTO may be eventually approved: treatment and relief of GERD symptoms in patients with erosive esophagitis and only in those unable to continue taking oral medication for a short- (up to 7 days) period.

4. I.V. doses other than 40 mg once-a-day are not recommended.

As an antisecretory, the 20 mg PANTO I.V. dose seems to be consistently inferior to the 40 mg I.V. dose of the drug and inconsistently effective when compared to the 40 mg PO.

Although doses of 80 or 120 mg I.V./day may be even more effective than the 40 mg I.V. under hypersecretory conditions such as in Z-ES patients (not the subject of this NDA), these higher doses of I.V. PANTO are not recommended because they are not needed since the majority of GERD patients **are not hypersecretors.**

May 27, 1999

/S/

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

cc:
NDA 20-988
HFD-180
HFD-180/LTalarico KMS for LT 5/28/99
HFD-180/HGallo-Torres
HFD-181/MWalsh
HFD-180/JChoudary
HFD-180/EDuffy
r/d 5/11/99 jgw
f/t 5/27/99 jgw
N/20988903.0HG

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL TEAM LEADER'S REVIEW

PROTONIX™ (pantoprazole sodium) for INJECTION
SAFETY UPDATE

NDA:	20-988
Submission Date:	March 31, 1999
Sponsor:	Wyeth/Ayerst Laboratories Philadelphia, PA
Route of Administration:	Intravenous
Pharmacological Category:	Antisecretory/Antiulcer/Anti-GERD Inhibition of the (H^+, K^+)-ATPase enzyme (proton pump) of the parietal cell in the gastric mucosa.
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

INDICATIONS AND USAGE

PROTONIX for injection is indicated for short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), as an alternative in patients who are unable to continue taking PROTONIX (pantoprazole sodium sesquihydrate) delayed-release tablets. Safety and efficacy of PROTONIX for injection as an initial treatment for GERD in patients who are able to take PROTONIX delayed-release tablets have not been demonstrated.

Material Reviewed:

This submission consists of 4 volumes. The update included new safety data with intravenous pantoprazole from Wyeth-Ayerst and Byk Gulden (licensor) studies. Presented were data obtained on other dosage forms, other dosage levels, other indications than those under review in the pending NDA and a brief summary of safety data for studies of pantoprazole enteric-coated tablets. Also submitted were labeling from 17 countries where registration approval for intravenous pantoprazole has been obtained.

Contents	Volume
Narrative review and tabular analyses of safety data; supportive tables	1
Electronic data for Protocol Nos. 304/308	2
Appendices; commercial marketing information	3
Case report forms for patients who died, discontinued due to an adverse event or who had a serious adverse event	4

EXECUTIVE SUMMARY

Summary Review of March 31, 1999 Safety Update

The safety information included in this SU report covered the period between the original NDA 20-988 data cut-off date (January 30, 1998) and November 30, 1998 for Wyeth-Ayerst (W-AR) studies. In addition, safety data were provided for all completed clinical studies conducted by Byk Gulden (B-G) Pharmaceuticals since the B-G data cut-off date for the original NDA (August 23, 1997), including all completed studies that were entered on the B-G clinical trial database and for which a final or interim clinical study report was available by August 23, 1998. The W-AR and B-G were not pooled with each other. Also included were data from spontaneous post-marketing reports and an unblinded interim analysis of safety data from ongoing oral pantoprazole maintenance studies 3001A1-302-US and -303-US (reviewed in detail in the SU for oral pantoprazole, NDA 20-987).

Although the main focus is on the information from the studies using I.V. pantoprazole, brief summaries of the safety data from the oral studies are presented.

The number of patients in W-AR pantoprazole studies included in the SU were:

Total n (Pts. Receiving Pantoprazole)	Study Identification
35 (35)	3001K1-304-US and 308-US [Zollinger-Ellison Syndrome] (Z-ES)

B-G pantoprazole I.V. studies were:

ORIGINAL NDA		UPDATE
A. Phase I: Short Infusions in Healthy Subjects		
257 (254)[a]	Many trials	26 (26) [FHP033 and –036]
B. Short Infusions in Special Populations		
21 (20)	FHP020 (renally impaired) FHP008 (liver impairment)	(NND)[b]
C. Continuous Infusion in Healthy Subjects		
39 (39)	4 Studies	(NND)[c]
D. Continuous Infusion in Patients with Bleeding Ulcers and in Healthy Subjects		
		31 (31) [BGSA012, FHP038 and –039]
E. GERD Acute Studies (I.V. PO)		
284 (284)	BAT010, FK3050	45 (45) FK3051

a) Total n (# receiving pantoprazole)
b,c) No new data on short infusion or continuous infusion in healthy subjects available.

In contrast to the original NDA, none of the patients exposed to I.V. pantoprazole from the W-AR studies during the SU reporting period were from the GERD acute population. Nonetheless, data from Z-ES patients administered very high doses of the drug (as much as 120 mg b.i.d. or 80 mg t.i.d. but usually 80 mg b.i.d. intravenously) were considered and contributed to the overall safety evaluation process. The B-G studies included patients from various populations, 45 of whom were from GERD acute study RK3051 where intravenous dosage was followed by oral administration of the drug (not the sequence of administration being sought).

The detailed review of the evidence presented in this SU, including incidence of withdrawals, deaths or serious AEs (none of which was attributed to pantoprazole) allows conclusions similar to those reached by the reviewer after appraisal of the safety data reported in the original NDA. This assessment did not reveal any disturbing findings or trends. Although the database is comparatively small due to the nature of the restricted potential I.V. indication, the safety pattern of intravenously administered pantoprazole is generally reassuring and suggests that clinically important conditions are not being missed. Particularly reassuring is the additional safety data with oral pantoprazole, considering the high bioavailability of the drug (77%). Borrowing from the extensive experience with the two approved PPIs, omeprazole and lansoprazole, no serious safety concerns are to be expected.

In conclusion, the reviewer agrees with the sponsor that the overall results in the initial NDA and the SU demonstrate that treatment with intravenous pantoprazole is safe and well-tolerated.

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I. CLINICAL DATABASE

In this update, a summary of safety information from W-AR studies obtained from January 30, 1998 (the NDA cut-off date) through November 30, 1998 (the SU cut-off date) is presented. The update provides safety data for 35 patients enrolled in 2 trials conducted by W-AR with I.V. pantoprazole in Z-ES patients. It is important to note that these studies in Z-ES patients did not evaluate patients with GERD unable to take oral PROTONIX™, the indication under current review in pending NDA 20-988. Further safety information was summarized from 7 trials of oral pantoprazole conducted by
W-AR in various patient populations. Also, supportive safety data were provided for completed clinical trials conducted by B-G Pharmaceuticals from August 23, 1997 (B-G NDA cut-off date) through August 23, 1998 (B-G safety update cut-off date). This included safety data on ca. 80 subjects/patients receiving I.V. pantoprazole added to the B-G database since the NDA cut-off date, from 6 clinical studies in various populations. It is worth noting that 23 patients were from an acute treatment study (FK 3051) of I.V./PO pantoprazole in patients with GERD. Further, a total of 26 subjects [from B-G PO/I.V. studies (FHP 0033 and FHP 0036)] were enrolled in phase I evaluations and previously discussed in the SU for oral pantoprazole (NDA No. 20-987).

The sponsor notes that side-by-side comparisons of data from this SU with that in the original NDA were provided for similar patient populations. Because the patient populations and treatment groups for the W-AR studies included in the original NDA were different from those included in the SU, side-by-side comparisons were not possible and only the safety update data were presented. However, side-by-side comparisons were provided for data from the B-G GERD acute I.V./PO study population. Side-by-side comparisons between data from the SU and data from the NDA were not provided for the Phase I/II trials. It should also be noted that B-G study FK0351 (GERD acute study) consisted of two treatment groups: One group received 40 mg/day of I.V. pantoprazole for the first 5 days followed by 40 mg/day of oral pantoprazole for the remainder of
8 weeks; the other group received 40 mg/day of oral pantoprazole for 8 weeks. Unlike similar I.V./PO studies with GERD patients originally presented in NDA No. 20-988, data from the I.V./PO treatment group of study FK3051 could not be separated by dosage form. Therefore, safety data from study FK3051 were presented separately for each treatment group, i.e., the I.V./PO and PO/PO groups, but data from the I.V. portion of the I.V./PO regimen were not presented separately.

II. TABLE OF CLINICAL STUDIES

This section [sponsor's Tables 2A (vol. 1, pages 9-12) and 2B (vol. 1, pages 13-22)] provided two long tables listing all clinical trials in the SU. From this information, Table 1 has been assembled. This Table gives a brief description of the main features of the study, including number of patients in each treatment group. Data from studies with oral pantoprazole were reviewed in SU of NDA 20-987 and are not included in Table 1.

TABLE I
NDA 20-988 SU

COMPLETED STUDIES WITH I.V. PANTOPRAZOLE (lyophile)

Protocol No. Report No. Investigator(s) (Country)	Study Design	Dose Route, Frequency (Duration of Treatment)	No. Enrolled in Study	Demographics
I. W-AR STUDIES				
Studies in Z-ES patients				
3001K1-304-US Multicenter US	OL, pantoprazole only, individual titration, inpatient study of the inhibition of gastric acid secretion in patients with Z-ES. Study includes 2-week prestudy screening, washout and run-in period, and up to 8 days at the inpatient unit.	Starting dose: 80 mg i.v. over 15 min. Subsequent doses titrated so that gastric acid output was <10 mEq/h (or <5 mEq/h for pts. with partial gastrectomy) for the hour before the next dose of pantoprazole. Maximum dose of 240 mg in a 24-h period. Test medication for a maximum of 6 days.	21 (4 additional patients withdrew during the washout period)	13 M, 8 F 29 to 75 y (51.9y) 4 B 16 W 1 H
3001K1-308-US Multicenter US	OL, pantoprazole only, individual titration, inpatient study of the inhibition of gastric acid secretion in patients with Z-ES.	Starting dose: 80 mg i.v. over 15 min. Subsequent doses titrated so that gastric acid output was <10 mEq/h (or <5 mEq/h for pts. with partial gastrectomy) for the hour before the next dose of pantoprazole. Maximum dose of 240 mg in a 24-h period. Test medication for a maximum of 6 days.	14	9 M, 5 F 30 to 67 (52.4 y) 2 B 12 W
II. B-G STUDIES				
A. GERD Acute Studies				
FK3051 (99/97) R. Fischer, MD Switzerland Single center	DB, randomized, parallel-group study to compare initial symptom relief of pantoprazole, either po, or i.v., in patients with reflux esophagitis. The study population consisted of patients with GERD grade II or III, or patients with severely intense symptoms typical of reflux esophagitis.	Pantoprazole lyophile: 40 mg/2 min, i.v., qd Placebo tablet: po, qd **Days 6-56:** Pantoprazole tablet: 40 mg, po, qd **Days 1-5:** Placebo lyophile: i.v., qd Pantoprazole tablet: 40 mg, po, qd **Days 6-56:** Pantoprazole tablet: 40 mg, po, qd	45 P	11 M, 12 F 28-88 (55 y) 10 M, 12 F 35-81 (57 y)

B. General PK Phase I Studies in Healthy Volunteers				
FHP036E (49/96) GMR-32396 Prof. I. Walter-Sack Germany	SB, randomized, two-period crossover study with an additional treatment (a) to investigate the PK and PD interaction between pantoprazole and glibenclamide (glyburide). Glucose and insulin levels were followed as dynamic markers.	a) Pantoprazole 40 mg, i.v., over 15 min. b) Pantoprazole 40 mg, po, qd, for 4 days. Day 5, pantoprazole 40 mg, i.v., over 15 min + Glibenclamide 3.5 mg, po c) placebo (entero-coated tablet) qd, for 4 days. Day 5, 0.9% NaCl solution i.v., over 15 min + Glibenclamide 3.5 mg, po	22 S	22 M 20-42 (28)
a. EMs of pantoprazole and PMs of pantoprazole				
FHP033 (24/98) W. Wurst, MD Germany	Parallel group design comparing extensive metabolizers (EM) and poor metabolizers (PMs) of pantoprazole	Day 1: Placebo Day 2 to 7: 40 mg, po, qd (Pantoprazole tablet) Day 8: 40 mg/15 min. i.v. (Pantoprazole, i.v.)	2 EMs 2 PMs	4 M 29 to 31 y (29 y) 4 W
b. Other				
BGSA012 (135E/97) C. Van Rensburg, MD South Africa	Open, single-center study to gain information about intragastric pH increase after an 80-mg loading dose of pantoprazole, followed by a long-term infusion of 8 mg/h of pantoprazole. Assess safety of long-term infusion in patients with endoscopically confirmed bleeding peptic ulcer.	Pantoprazole lyophile formulation 40 mg/vial: injection of 80 mg/2 min followed by continuous infusion of 8 mg/h over 72 h (days 1 to 3) and 40 mg/2 min, bid (days 4 to 7)	20	8 F, 12 M 27 to 70 y (48 y)
FHP038 (202/97) W. Wurst, MD Germany	Open study to gain information on the effect of long-term infusion of pantoprazole after a loading dose on intragastric pH and to assess the safety in patients with BPU. The study population consisted of patients with active bleeding peptic ulcer (Forrest Ia, Ib, IIa), endoscopic hemostasis with adrenalin, and who had started treatment with pantoprazole and pH-metry within 2 h after endoscopic hemostasis.	Pantoprazole lyophile formulation 40 mg/vial: 80 mg/2 min loading dose followed by continuous infusion of 8 mg/h over 0 to 72 h followed by pantoprazole 40 mg/2 min. bid (days 4 to 7).	2	F 54 and 90 y
FHP039 (140/97) W. Wurst, MD Germany	Open, randomized, two-period crossover study to assess the increase in intragastric pH after an 80-mg loading dose of pantoprazole administered as a 2-min injection vs. 2-h infusion at the start of a 24-h long-term infusion of pantoprazole 8 mg/h.	Pantoprazole lyophile formulation 40 mg/vial a) i.v. injection of 80 mg/2 min followed by continuous infusion of 8 mg/h over 24 h. b) I.V. infusion of 96 mg/2 h followed by continuous infusion of 8 mg/h over remaining 22 h.	9	4 F, 5 M 25 to 32 y (30 y)

This Table corresponds to sponsor's Tables 2A and 2B, with extensive modifications.

W-AR=Wyeth-Ayerst; B-G=Byk Gulden; OL=open label, Z-ES=Zollinger-Ellison syndrome patients. GERD=gastroesophageal reflux disease; DB=double-blinded; PK=Pharmacokinetic; PD=Pharmacodynamic; SB=single blinded; EMs=extensive metabolizers; PMs=poor metabolizers; BPU=Bleeding Peptic Ulcer.

II. EXTENT OF EXPOSURE TO TEST MEDICATION (TABLE 2)

As noted above, in contrast to the original NDA, none of the patients exposed to pantoprazole from the W-AR I.V. studies during the SU reporting period were from the GERD acute population. During the SU period, 9 patients with Z-ES were enrolled at different times in W-AR studies 3001K1-304-US and -308-US because of the rarity of the disease. In addition, 12 patients received I.V. pantoprazole during W-AR study 3001K1-304-US and 5 patients received I.V. pantoprazole during W-AR study 3001K1-308-US.[1] Drug exposure was not presented for the B-G studies.

TABLE 2
NDA 20-988 SU

CUMULATIVE[a] DURATION OF EXPOSURE OVER TIME
(W-AR STUDIES 3001K1-304-US AND -308-US)

	CUMULATIVE DURATION OF EXPOSURE (in days), n (%)							
Dose	**<1**	**≥1**	**≥2**	**≥3**	**≥4**	**≥5**	**≥6**	**≥7**
Any	35	35	35	35	32	31	31 (89%)	1
80 mg BID	30 (86%)	30	30	30	28	27	27 (90%)	
120 mg BID	3	3	3	3	2	2	2	
80 mg TID	2	2	2	2	2	2	2	1

NONCUMULATIVE[b] DURATION OF EXPOSURE OVER TIME
(W-AR STUDIES 3001K1-304-US AND -308-US)

	NONCUMULATIVE DURATION OF EXPOSURE (in days), n			
Dose	**3**	**4**	**6**	**7**
Any	3	1	30	1
80 mg BID	2	1	27	
120 mg BID	1		2	
80 mg TID			1	1

a) **Cumulative exposure** = number of patients who took the drug *for at least* the time interval defined.
b) **Noncumulative exposure** = number of patients who took the drug *for exactly* the time interval defined.

In these studies dose and dose frequency were adjusted to determine the regimen required to decrease and maintain acid secretion at <10 mEq/h in patients who had not undergone acid-reducing surgery, and at <5 mEq/h in patients who had undergone such surgery. The maximum duration of treatment with I.V. pantoprazole was to be 6 days.

IV. DEMOGRAPHY

The sponsor presented these data in Tables 4.1A (vol. 1, page 28) and 4.2.1A (vol. 1, page 30). In summary,

[1] The difference between the studies is that for study 3001K1-304-US, patients underwent a washout from acid-suppressant therapy before receiving pantoprazole whereas for study 3001K1-308-US, patients did not undergo a washout period. Because of this difference between studies, patients who participated in both studies are counted twice throughout the SU.

- In the W-AR Z-ES studies (3001K1-304 and –308-US), 35 patients, 13 M and 22 F, were enrolled; age range was 18 to 64 y (mean 52.1 ± 12.1 y).

- In the Byk Gulden I.V./PO GERD acute study (FK3051), 45 patients, 24 F and 21 M, were enrolled; age range was 28 to 88 y (mean 55.4 ± 15.2 y). Of the 45 patients enrolled, 22 received oral pantoprazole only and 23 received I.V. plus oral pantoprazole.

- Two (2) Byk Gulden continuous infusion studies in patients (BGSA012 and FHP038) and 1 continuous infusion study (FHP039) in healthy subjects were conducted to study the effects on gastric pH. In study BGSA012, 20 patients, 8 F and 12 M, ranging in age from 27 to 70 y (mean 46.7 ± 11.0 y) were enrolled. In study FHP038, 2 F patients who were 90 and 54 y of age were enrolled. In study FHP039, 9 healthy subjects, 5 M and 4 F, ranging in age from 25 to 32 years (mean 29.7 ± 2.0 y) were enrolled.

V. DEATHS AND PREMATURE DISCONTINUATIONS

A. Deaths[2]

- No deaths were reported from W-AR I.V. studies.

- Deaths were reported for:
-

a) 3 patients (30267-0005=drug and alcohol overdose; 30271-0007=prostatic adenocarcinoma; and 30275-0002=acute anterior M.I.) from the W-AR oral studies. None of these deaths were considered related to pantoprazole

and

b) 11 patients (2 given I.V. and 9 given oral pantoprazole). Again, none of these deaths were considered related to pantoprazole.

B. Premature Discontinuations

Summarized below are the reasons for these D/Cs: 2 were apparently due to treatment-emergent AEs (headache, pruritus) and 2 to insufficient therapeutic effect (G.I. rebleeding).

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[2] Deaths during both the W-AR studies and the Byk Gulden studies were summarized in sponsor's Table 6.3A (vol. 1, page 44). None of the deaths from the W-AR studies occurred during I.V. therapy.

Narratives describing the causes of death for patients from the W-AR studies who received oral therapy were provided in sponsor's Appendix 1 (Patient Narratives for Serious AEs, Discontinuations due to Adverse Events, and Deaths) of the SU for oral pantoprazole. One (1) patient from the Byk Gulden ongoing clinical studies and 1 patient from the Byk Gulden observational studies died during I.V. therapy. The CIOMS for each of these patients were provided in sponsor's Appendixes 3 and 4, respectively. CIOMS for patients who received oral therapy and died during the Byk Gulden postmarketing experience, observational studies, and ongoing clinical studies were provided in sponsor's Appendixes 7, 8 and 9, respectively, of the SU for oral pantoprazole.

Patient I.D./Study	Comment
30493 (W-AR Z-ES studies) [received 120 mg BID starting dose]	W/D from therapy at his own request, likely due to **headache**.
FK3051-39 (I.V./PO GERD B-G study) [41y old woman received 40 mg of the drug]	W/D because of **pruritus**
Pts. #4 and #20 (BGSA012 continuous infusion study) [both received injection of 80 mg/2 min. followed by continuous infusion of 8 mg/h over 72 h.]	W/D because of **G.I. rebleeding** W/D because of **G.I. rebleeding**

IV. ADVERSE EVENTS

- During W-AR studies in patients with Z-ES (3001K1-304-US and –308-US) the incidence of AEs during I.V. treatment was as follows.

	[n=35]
Pts. with at least one AE	27 (77%)
Most common events with 80 mg BID	
Headache	8 (27%)
Diarrhea	5 (17%)
Insomnia	5 (17%)
Local Rx. to procedure	5 (17%)
Considered drug-related	10 (33%)

- During the Byk Gulden I.V/PO GERD acute study (FK3051), 5 (22.7%) patients who received oral pantoprazole only and 6 (26.1%) who received I.V. + oral pantoprazole had an AE.
  - **Asthenia** (13%) was the most common event among patients who received I.V. + oral pantoprazole.
  - No serious adverse events were reported.

- During Byk Gulden continuous-infusion study BGSA012, 10 of the 20 patients reported AEs. Events that occurred in more than 1 patient were:

  thrombophlebitis of the arm (n=4)
  rebleeding of ulcer (n=2)
  headache (n=2) and
  constipation (n=2).

Three (3) patients had AEs that were considered to be serious but unrelated to treatment. Neither patient in continuous-infusion study FHP038 had an adverse event. In continuous infusion-study FHP039, 1 healthy subject reported 2 AEs, a headache and nausea.

VII. RESULTS OF CLINICAL LABORATORY EVALUATIONS

These data, presented in sponsor's Tables 7.1A (vol. 1, page 47), 7.1B (vol. 1, page 48), 7.2A (vol. 1, page 49) and 7.2.1A (vol. 1, page 50), are summarized below.

- During the W-AR I.V. Z-ES studies, no pattern was observed in the incidence of potentially clinically important laboratory results. Mean changes from baseline in laboratory values were occasionally statistically significant for various parameters; however, these changes were not clinically important.

- During the Byk Gulden acute GERD I.V./PO study, the incidence of potentially clinically important laboratory results at baseline and follow-up were similar.

- No laboratory data were provided for continuous infusion studies with patients [GBSA012, FHP038 (n=9) and FHP039 (n=2)].

VIII. VITAL SIGNS, BODY WEIGHT AND EKG DATA

Data presentation was limited to studies conducted by W-AR because B-G did not systematically collect and/or analyze vital sign or weight data in their studies. The information was presented in sponsor's Tables 8.1A (vol. 1, page 51), 8.1B (vol. 1, page 51), 8.1C (vol. 1, page 52) and 8.1D (vol. 1, page 52).

- 5 of the 30 patients who received the 80-mg BID dose had potentially clinically important increases in diastolic BP and 3 had potentially clinically important increases in systolic BP.

- 1 patient had a potentially clinically important increase in diastolic BP in both studies 3001K1-304-US and –308-US so that in actuality, 4 patients had a potentially clinically important increase in diastolic BP and 1 patient had an increase in diastolic BP in either study.

- But these increases in BP were neither sustained nor apparently dose related [none of the 2 patients given 80 mg TID experienced clinically significant changes in BP].

- 1 patient had a potentially clinically important decrease in body weight.

- None of the changes in vital signs, were considered by the investigator or medical monitor to be clinically important. The reviewer agrees with this conclusion.

- None of the reported EKG changes, which included L atrial enlargement and First degree heart block and sinus bradycardia were considered to be clinically important in the judgment of the investigator.

IX. STUDIES OF ORAL PANTOPRAZOLE

Data from the W-AR studies (3001A2-305-US and –306-US=H. pylori eradication studies; -302-US and –303-US=GERD maintenance studies; and 3001A1-307-US=Z-ES study) are very briefly summarized below. Although additional safety information was available, drug exposure by dose and time interval was not presented for the B-G studies because overall exposure to pantoprazole in the population of interest, acute GERD patients, increased by <10% during the SU period.

- From the review of this evidence (review of SU for oral pantoprazole), the reviewer concluded that the findings from the W-AR and B-G clinical studies using oral pantoprazole during the SU reporting period were similar to those reported in the original NDA. Occasional differences in the incidences of AEs during the W-AR studies were most likely due to the longer duration of exposure during the (still unblinded) GERD maintenance trials than during the GERD acute studies. The reviewer agrees with the sponsor, conclusion: the overall results showed that treatment with pantoprazole tablets was safe and well tolerated.

X. SPECIAL SAFETY CONSIDERATIONS: OPTIC EVENTS

Concerns raised in Europe about a possible relationship between the administration of I.V. omeprazole (not available in the U.S.) and visual disturbances have become concerns for the drug class as a whole. The information provided in the SU originated from W-AR and B-G studies.

- The W-AR medical monitor reviewed the database for the SU reporting period to identify any optic events reported as AEs. In their Table 11.2.1A (vol. 1, page 73) the sponsor identified all the patients from the W-AR studies who had optic events that were associated with AEs.

  From this detailed information, the following is concluded:

  - All events occurred during oral therapy and were mild or moderate.
  - None of the events was associated with anterior ischemic optic neuropathy.

- To prepare a comprehensive review of optic events during treatment with pantoprazole, B-G searched its database[3] for events during the period from 1 Jan 1998 to 23 August 1998 with the following WHO-ART OPTIC EVENT SEARCH TERMS (codes):

Code	Term	Code	Term	Code	Term
0130	Neuropathy	0159	Visual field defect	0243	Eye abnormality
0135	Optic atrophy	0227	Glaucoma	0257	Vision abnormal
0136	Optic neuritis	0241	Diplopia		

- 59 patients with events in these categories were identified using this search method. These 59 patients and their events were listed in the following sponsor's tables.[4]

Table	
11.2.2A	14 spontaneous post-marketing reports received from the over 4 million (vol. 1, page 75) patients prescribed oral pantoprazole.
11.2.2B (vol. 1, page 76-77)	37 patients reporting optic events while taking oral pantoprazole in post-marketing (observational) studies [from a total n of 50,000 patients].
11.2.2C (vol. 1, page 78)	8 patients reporting optic events while taking oral pantoprazole during clinical trials

Both the optic event as well as any concurrent events of a non-optic nature were identified in these tables.

- All the optic events occurred during oral therapy.
- Overall, most of the optic events were mild and transient.

XI. SERIOUS SPONTANEOUS POST-MARKETING REPORTS

- The sponsor noted that the Worldwide Clinical Drug Safety Surveillance (WWCDSS) database is maintained by W-AR to identify spontaneously reported serious events from clinical trials and post-marketing exposure, including studies sponsored by W-AR and affiliates, or conducted under investigator-sponsored INDs. The eight 15-day reports filed during the SU reporting period were described in sponsor's Table 12.1A (vol. 1, page 81); all of these events occurred during I.V. pantoprazole therapy.

[3] B-G maintains a database known as CARE as part of their worldwide drug safety surveillance system. This database contains detailed reports (CIOMS reports) on AEs reported by patients taking pantoprazole as part of a clinical trial, a post marketing study, or as a marketed drug (i.e., spontaneously reported by a prescribing physician).
[4] The CIOMS for patients with optic events during post-marketing experience, during observational studies, and during clinical studies were shown in sponsor's Appendixes 4, 5, and 6, respectively, of the SU for oral pantoprazole.

- Sponsor's Table 12.2A (vol. 1, pages 83 and 84) listed the serious post-marketing adverse events that were reported to B-G during the SU reporting period. Their Table 12.2B (vol. 1, pages 85 through 88) listed serious events reported during the SU reporting period from the observational studies. None of the serious post-marketing events occurred during I.V. therapy.

    - 2 patients,[5] 305-98-0340 and 305-98-1522, from the observational studies had serious events during I.V. therapy. These events were not attributed to I.V. pantoprazole.

- Serious events that occurred during the ongoing B-G clinical studies were shown in sponsor's Table 12.2.1A (vol. 1, pages 90 through 97).

    - 6 patients had serious AEs during I.V. therapy. There was no apparent temporal relationship between I.V. drug administration (<2 minutes) resulting in high blood levels of the drug and the event.[6] The latter occurred at least 3 days later after administration of test medication.
    - 7 patients died during the ongoing studies. None of the deaths were related to treatment with pantoprazole.

From his review of the evidence, the reviewer agrees with the sponsor's conclusion:

"In the spontaneous reports during the safety update reporting period, no patterns of events or laboratory abnormalities were identified that could causally be related to treatment with pantoprazole. Complaints associated with gastrointestinal disorders were likely associated with pre-existing pathology."

XII. UPDATE OF COMMERCIAL MARKETING EXPERIENCE

As of August 23, 1998, B-G Pharmaceuticals has received registration approvals for I.V. pantoprazole in 17 countries. These include: the U.K. (December 4, 1996) and Germany (July 31, 1997). The I.V. formulation is marketed in the 9 countries listed below (the registration date is given):

[5] The CIOMS for these 2 patients were provided in sponsor's Appendix 3. The CIOMS for the patients with serious events who received oral therapy during the post-marketing period, observational studies, and ongoing clinical studies were shown in sponsor's Appendix 7, 8, and 9, respectively, of the SU for oral pantoprazole.

[6] The CIOMS for these patients were provided in sponsor's Appendix 4. The CIOMS for patients with serious event during oral therapy were shown in sponsor's Appendix 9 of the SU for oral pantoprazole.

Registration Date	Indications
Finland (Feb. 9, 1998)	GERD (moderate and severe) DU, GU
Austria (March 13, 1998)	GERD (moderate and severe) DU, GU
Belgium (June 18, 1998)	GERD (moderate and severe) DU, GU
Denmark (March 23, 1998)	GERD (moderate and severe) DU, GU
Germany (July 31, 1997)	GERD (moderate and severe) DU, GU
Netherlands (February 11, 1998)	GERD (moderate and severe) DU, GU
France (February 24, 1998)	Gastric antisecretory treatment if oral administration is **not** possible
Mexico (March 30, 1998)	GERD (moderate and severe) DU, GU
Spain (April 3, 1998)	GERD (moderate and severe) DU, GU

- During the update period no regulatory authority requested changes in the labeling as a result of safety or efficacy issues. The product has not been withdrawn from the market for safety reasons in any country. No countries where I.V. pantoprazole is approved/marketed had revisions to their I.V. pantoprazole labeling during the update period.

July 1, 1999

/S/

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

cc:
NDA 20-988
HFD-180
HFD-180/LTalarico 7.6 99
HFD-180/HGallo-Torres
HFD-181/MWalsh
HFD-180/JChoudary
HFD-180/EDuffy
HFD-103/FHoun
HFD-103/VRackowski
r/d 6/30/99 jgw
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NOV 19 1999

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-988
Sponsor:	Wyeth-Ayerst Research (W-AR) Philadelphia, PA
Date Submitted:	August 31, 1999
Drug:	PROTONIX® (pantoprazole sodium) for Injection
Pharmacological Category:	Gastric Acid Antisecretory, Anti-GERD, Anti-ulcer. Inhibitor of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell
Approved Indication:	Short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), as an alternative in patients who are unable to continue taking PROTONIX® (pantoprazole sodium sesquihydrate) Delayed-Release Tablets.
Formulation/Mode of Administration:	Freeze dried powder for reconstitution in a 40 mg/ vial strength for I.V. administration.
Material Reviewed:	W-AR submission dated August 31, 1999 in response to the Agency's July 20, 1999 approvable letter which included recommended revisions to the draft Draft Package Insert.
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D. Medical Team Leader

I. BACKGROUND

Pantoprazole is an inhibitor of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. In FDA Action Letter of July 20, 1998, W-AR was informed that PROTONIX® (pantoprazole sodium) for Injection, NDA 20-988, is approvable. The indication is for the short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), as an alternative in patients who are unable to continue taking PROTONIX® (pantoprazole sodium sesquihydrate) Delayed-Release Tablets. The July 20, 1999 FDA action letter to sponsor

indicated that the safety and efficacy of PROTONIX® for Injection as an initial treatment for GERD have not been established. W-AR was informed that before this NDA is approved it was necessary to obtain approval for NDA 20-987, PROTONIX® (pantoprazole sodium sesquihydrate) Delayed-Release Tablets. In addition, before approval, it was necessary for the sponsor to address several issues, including labeling and chemistry.

In their August 31, 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 labeling section under consideration. 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, Recommendation for Regulatory Action)**. The latter includes a recommendation to either accept or reject the change proposed by W-AR and a justification in support of the reviewer's recommendation. Per FDA request, the term "for Injection" has been incorporated into the product name. W-AR notes that the results presented in W-AR GTR-33231, as revised, (provided in Attachment G, Appendix 9 of the August 31, 1999 submission) and Byk Gulden Report 310-EST-1996 (provided in Volume 1.005 of the original NDA submission) support the conclusion that it is not necessary to protect the reconstituted or admixed solutions from light. This statement is included in the package insert in the Dosage and Administration section.[1]

> **NOTE:** Changes throughout the labeling to provide the product description "for injection" which has been added to the trade name, are usually not commented upon. It is to be noted that the "I.V." designation has been retained to insure that the product is administered parenterally by the route established to be safe and effective on both W-AR and B-G's studies. The present review does not contain the customary (usually separate) section on Recommendations for Regulatory Action at the end because these are given throughout.

a. <u>Paragraphs 26 through 29 (Clinical Studies)</u>

<u>Paragraph 26</u>

All changes recommended by the Agency have been made. Day 10, day 1 and day 7 have been added in parenthesis, immediately after the phrases last day of oral medication, the first day, and the last day of i.v. administration, respectively.

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[1] Also, per our request, other changes were made to the immediate container and carton labels. The caution statement "Reconstituted product should not be frozen" was added. As presented in the sponsor's May 13, 1999 immediate container and carton label submission, the statement "Protect from Light" is placed on a separate line. In addition, the description "10 mL fill," before 12 mL vial was incorporated for internal quality assurance purposes. As mentioned above, it is not necessary to add a cautionary statement regarding protecting the admixed solution from light to the immediate container or carton labels.

W-AR Rationale

The sponsor states that these additions provide further clarification to the statements made in this paragraph.

COMMENT (RFRA)

These (minor) additions are acceptable as they indeed add further clarification regarding the study days on which assessments - in these erosive esophagitis patients - were made.

Paragraphs 27 and 28

FDA Comments/Revisions	W-AR Comments/Revisions

Parameter	ORAL PROTONIX DAY 10	PROTONIX I.V. DAY 7	Placebo IV DAY 7
Maximum acid output	6.49 n=30	6.62 n=23	29.19* n=7
Basal acid output	0.80 n=30	0.51 n=23	4.14* n=7

*P<0.0001 Significantly different from PROTONIX I.V.

ANTISECRETORY EFFECTS (mEq/h) OF 40 mg PROTONIX I.V. FOR INJECTION AND 40 mg ORAL PROTONIX IN GERD PATIENTS

Parameter	PROTONIX Delayed Release Tablets DAY 10	PROTONIX I.V. for Injection DAY 7[a]	Placebo I.V. DAY 7
Mean ~~m~~Maximum acid output	6.49 n=30	6.62 n=23	29.19* n=7
Mean ~~B~~basal acid output	0.80 n=30	0.51 n=23	4.14* n=7

*P<0.0001 Significantly different from PROTONIX I.V. for Injection
a: The antisecretory effects of 40 mg of PROTONIX I.V. for Injection were similar on day 1 and day 7.

the 20-mg and 40-mg groups at a one-sided α-level of 0.025. In each case, the statistical test led to rejection of the null hypothesis. Therefore, we conclude that the acid output for the intravenous form is not more than % greater than that of the oral form and the two forms of pantoprazole are pharmacologically equivalent.

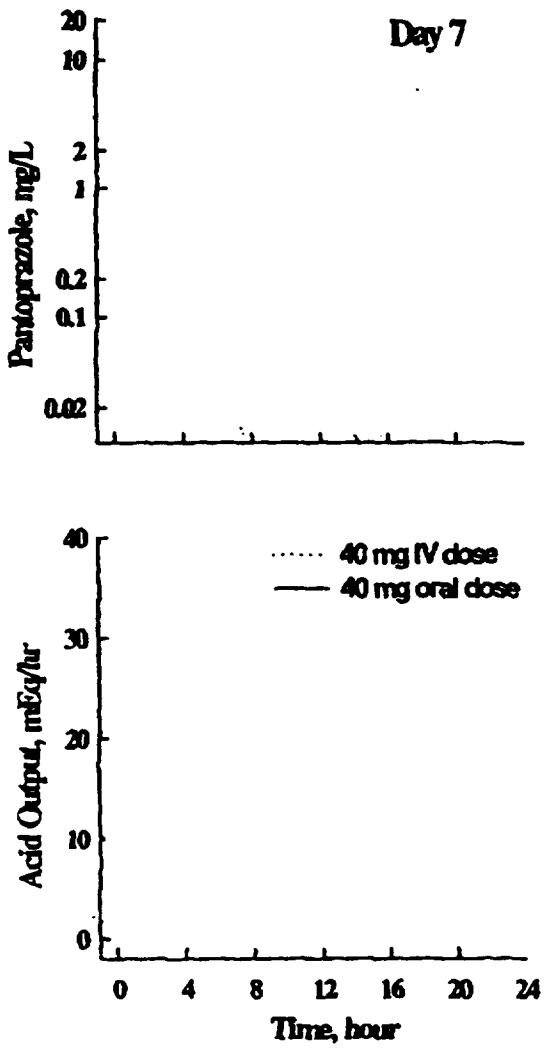
"The suppression of acid output observed in Study No. 309 is also pharmacodynamically consistent with study results from the Study No. 100 conducted in normal volunteers and which were presented in the NDA. This can be demonstrated by extending the PK/PD model (based on the results of Study No. 100) as presented in the NDA. First, plasma concentrations are simulated for day 7, incorporating the % bioavailability data of the oral dosage form (see attached figures). Then, the corresponding acid output at steady state is simulated based on the model for both intravenous and oral administration. These simulated data add further support that pharmacodynamic equivalence exists, as acid output is suppressed within the range of mEq/hr for both routes of administration in the same steady state dosing interval."

The two main changes proposed by the sponsor are: a) addition of "is pharmacologically equivalent to the 40-mg delayed-release tablet" while deleting the words ___ and b) the addition of footnote a to the Table. This footnote reads "a: The antisecretory effects of 40 mg of PROTONIX I.V. for injection were similar on day 1 and day 7".

W-AR Rationale

In support of these proposed changes,

Pantoprazole plasma concentrations and acid output simulated after multiple, daily, 40 mg I.V. and oral doses



In paragraph 28, W-AR proposes

Comment (RFRA)

The sponsor's lengthy rationale in support of the proposed changes requires careful consideration of the facts evaluated in the MOR of NDA 20-988 (May 28, 1999). Particular emphasis is put on results of pivotal trial 30001K1-309-US. Several of the sponsor's statements are indeed accurate. In the main, the trial tested the hypothesis that 40 mg PANTO I.V. formulation is equivalent to 40 mg oral PANTO in the suppression of basal and maximal acid secretion in erosive esophagitis patients. So, the trial was set to compare the BAO and the maximum pentagastrin-stimulated acid output (MAO) in patients with a history of erosive esophagitis who were switched from oral to I.V. PANTO formulation. The main conclusion from the study was that when results on Day 7 were assessed, the 40 mg I.V. once-a-day dose of the drug can maintain the same degree of antisecretory activity already obtained after a 7-day regimen of orally administered 40 mg. The trial results are summarized in the above displayed Table.

However, of the two parameters evaluated, the mean BAO (mEq/h) was >20% higher with the oral (0.80) than the I.V. formulation (0.51). So, technically speaking, although the formulations can be said to be bioequivalent for MAO (6.49 vs 6.62, <20% difference) they are similar (but not equivalent) for BAO since 0.80 is >20% than 0.5[2]. Conclusions based on these comparisons are more meaningful because most GERD patients are not hypersecretors; BAO describes the secretory/antisecretory condition of the GERD patient more adequately than MAO.

An additional reason not to accept the sponsor's proposal in paragraph 27 is that in their proposed wording, no mention is made that one is talking about bioequivalence for Day 7 comparisons exclusively (Table 6 in MOR of May 28, 1999). As shown in Table 7 of the May 28, 1999 MOR, for the comparison $MAO_{FI.V.}$ vs MAO_{LPO} (first day i.v. vs last day oral) no equivalence was demonstrated. This lack of equivalence was shown regardless of the study population analyzed or the statistical test used to assess significance. This is an important finding. These results showed that PANTO I.V. cannot be recommended for use (where the GERD patient may need to be treated with the PPI from the start). This is because PANTO I.V. did not produce the same PD effect on the first day of administration in comparison to the 40 mg PANTO PO ($MAO_{FI.V.}$ vs MAO_{LPO} as well as $BAO_{FI.V.}$ vs BAO_{LPO}).

It is also recommended not to accept the footnote to the Table, identified as a. The sponsor claims that the antisecretory effects of 40 mg of PROTONIX® I.V. for Injection were "similar" on day 1 and day 7. However, as shown in Table 8 of the MOR of May 28, 1999 a more adequate description of MAO values is that these comparisons yielded inconsistent results: except for the sign test in the M-ITT, most p-values were either N.S. or borderline (approaching significance). Similarly, inconsistent results were obtained from BAO comparisons (see page 49 of MOR of May 28, 1999). Although in all three study populations (ITT, M-ITT and VFE) the p-values were significant on the t-test, all other comparisons (except t-test for ITT) yield N.S. results.

In summary, it is recommended to accept the addition of the word mean (MAO and BAO) to the Table above. Approval is not recommended of the sponsor's proposed revisions to paragraph 27

[2] Indeed, according to Table 9 of the MOR of May 28, 1999, all p-values (whether t-test, sign test or signed-Rank test) in all study population analyses (whether ITT, M-ITT or VFE) were **statistically significant**.

(claiming pharmacological equivalence instead of similarity between the I.V. vs the oral dosage form) or paragraph 28 (claiming similarity in antisecretory effects between days 1 and 7 for the PROTONIX® I.V. for Injection).

b. Paragraphs 30 and 31 (INDICATIONS and USAGE)

The sponsor proposes to remove in the first sentence and in the second, and add for more than 7 to 10 days. These are all very important revisions to the labeling.

W-AR Rationale

In support of these changes, the sponsor provides

Comment (RFRA)

It is recommended not to accept this change, for a number of reasons already mentioned in the above comments (R_sFRA). The sponsor's intent is to get approval of a **new indication**. Matters related to this additional indication were discussed in detail in several sections of the MOR of NDA 20-988 (May 28, 1999). On page 26 of this review under section **IX. CRITICAL TRIALS IN NDA 20-988**, a list of seven questions, to be answered at the end of the assessment of the evidence, was given. Reference is made to question No. 7: which is the question at the heart of the sponsor's request.

On page 28 of the May 28, 1999 MOR, results of two trials, where the test medication was given from the start is summarized. It was concluded that, efficacy wise, these 2 studies (BAT010 and FK3050) were inadequate to support the additional indication. For this reason, the results of these 2 incomplete studies were not even reviewed. Further discussion on this matter is given on paragraph 4, page 90 of the May 28, 1999 MOR. It was concluded that 40 mg I.V It is worth noting that results of critical study 309-US showed that this dose of PANTO does not produce the same PD effect on the **first day** in comparison to the 40 mg PANTO PO ($MAO_{F.I.V.}$ vs MAO_{LPO} and $BAO_{F.I.V}$ vs BAO_{LPO}). The drawn conclusions was that PANTO 40 mg I.V. can, most certainly, be recommended as an alternate to those GERD patients who are already on PANTO 40 mg PO (and hence the wording **...in**

patients who are unable to continue taking PROTONIX...tablets). However, the I.V. dosage form of the drug cannot be recommended in instances where the GERD patient may need to be treated parenterally from the start . It was again mentioned that the two studies submitted by the sponsor in support of the expansion of the requested indication, BAT010 and FK3050, did not use useful designs (Table 2 of MOR of May 28, 1999). It was reiterated that results of these inadequate studies were not assessed in that review.

c. Paragraphs 32 through 34 (CONTRAINDICATIONS, PRECAUTIONS, General, Information for Patients)

Accepted or no changes.

d. Paragraphs 35 through 38 (Drug Interactions)

To be assessed by Biopharm.

e. Paragraphs 39 through 44 (Carcinogenesis, Mutagenesis, Impairment of Fertility)

To be assessed by Pharm/Tox.

f. Paragraphs 45 (Pregnancy Teratogenic effects, Pregnancy Category B) and 46 (Non-teratogenic Effects)

To be assessed by Pharm/Tox.

g. Paragraph 47 (Nursing Mothers)

No change.

h. Paragraph 48 (Pediatric Use)

Acceptable (minor change).

i. Paragraphs 49 (Use in Women) and 50 (Use in Elderly)

Revisions accepted by the sponsor

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

Draft Labeling

W-AR Rationale

The sponsor's rationale is reproduced below:

Comments (RFRA)

With one exception or two (see below), the changes to the ADVERSE REACTIONS section of the PI, requested by the sponsor, are acceptable. The sponsor incorporated Agency-requested changes/deletions in paragraphs 51, 52 (deletion of Table) and 53 (this information was incorporated in paragraph 51). In paragraph 54, deletions were made where indicated by FDA in those cases where the event could be considered as an extension of the underlying condition and this is acceptable. However, the sponsor proposes to retain three events because their occurrence could not be considered related to the underlying disease. These include leg cramps, laryngitis and ear disorder. Upon reconsideration, the reviewer still proposes to delete leg cramps. There is no plausible reason to propose that this adverse event is associated with pantoprazole, a drug which primary pharmacological effect is to inhibit gastric acid secretion. Water and electrolytes changes, which sometimes are asssociated with leg cramps, have not been reported with use of PANTO (or other PPIs), furthermore, there is no known H^+/K^+ ATPase in the legs. Similarly, there is no known mechanism to propose that PANTO may produce inflammation of the laryngal but the reflux of acid associated with GERD may sometimes damage the upper respiratory system and produce laryngitis. Again, upon reconsideration, the sponsor may want to retain the

term "ear disorder" since hearing disturbances (broad term) may be, sometimes, due to PPI intake.

In paragraphs 55 and 56, the mentioning of the dosage range (up to 240 mg per day) and the update of the number of patients who have received the drug worldwide (11,100) respectively, are both acceptable. Other changes/revisions are indeed consistent with the package insert for PROTONIX Delayed-Release Tablets. The reviewer agrees with the sponsor's explanations regarding all of these revisions, reorganizations, and further changes in reference to paragraphs 59 through 75 and 76, postmarketing reports, as well as the accepted changes to paragraph 77 (laboratory values = no further changes requested).

k. Paragraphs 78-81 (Overdosage)

W-AR Rationale

The sponsor noted that in paragraph 78, changes were made in accordance with the Agency's request. In paragraph 81, the only revisions to FDA's paragraph were the mouse and rat values. In mice, the lowest intravenous (I.V.) dose of pantoprazole causing lethality was 378 mg/kg (expressed as the free acid) rather than 355 mg/kg. In rats, the lowest I.V. dose of pantoprazole causing lethality was 230 mg/kg (expressed as the free acid) rather than 222 mg/kg.

Comments (RFRA)

It is recommended to accept these sponsor's proposed revisions. They are based on study reports of evaluations in mice (GTR-31633 and –31637) and rats (GTR-31640, -31638, -32136 and –31650). This proposed revision to the labeling should also be assessed by Pharmacology/Toxicology.

l. Paragraphs 82 through 86 (DOSAGE AND ADMINISTRATION)

W-AR Rationale

Explanations provided by the sponsor are summarized here. It is noted that revisions in paragraph 82 reflect recommendations by the Agency for the first three sentences. However, the fourth sentence has been changed to be consistent with the Indications sections, i.e.,

An additional caution is added regarding the use of parenteral routes other than the intravenous route of administration in the last sentence of paragraph 82. Paragraph 83 was not included, since the information regarding patient with liver impairment is presented in more detail in paragraph 84. This paragraph as composed is consistent with the information provided in paragraph 13 (Hepatic Impairment).

In paragraph 85, the information presented is consistent with the digoxin information previously provided in paragraph 14 (Drug-Drug Interactions).

In paragraph 86, a statement is added that [ ]This information is based on data obtained from two reports.[3]

Comments (RFRA)

The revisions in paragraph 82, indeed, reflect recommendations by the Agency for the first three sentences. The sponsor proposes to change the fourth sentence of this paragraph "to be consistent with the Indications sections". As repeatedly mentioned in this review, the indication for I.V. PROTONIX is for patients unable to take the oral dosage form; efficacy under conditions of _____ use has not been demonstrated. Thus the message to the physician summarized in the fourth sentence of the FDA version of the labeling "Safety and efficacy of PROTONIX I.V. for injection as initial treatment for GERD have not been demonstrated (see INDICATIONS and USAGE) is factual. This important information should not be modified until the sponsor submits clinical evidence that PROTONIX I.V. is efficacious when given from the start. It is recommended to accept the addition of the sentence "parenteral routes of administration other than I.V. are not recommended", as well as those changes to paragraphs 83 through 85 dealing with PKs of the drug in liver impairment and concomitant use with digoxin. Both paragraphs are consistent with information provided in paragraph 13 (Hepatic Impairment) and 14 (reference to digoxin under Drug-drug interactions). The revision regarding no need to protect from light has been properly documented in two reports. Nonetheless, this proposed revision to the labeling should be assessed by Chemistry.

/S/ November 18, 1999

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

cc:
NDA 20-988
HFD-180
HFD-180/LTalarico
HFD-180/SAurecchia
HFD-103/F. Houn
HFD-180/HGallo-Torres
HFD-181/PM
HFD-180/JChoudary
HFD-180/LZhou
r/d 10/28/99 jgw
f/t 11/18/99 jgw
N/20988910.0HG

LT 11-19-99

[3] [Reconstituted Pantoprazole Lyophile 40 mg: Use-Life and Test of Interaction with Primary Packaging Material." (Byk Gulden Report dated 8/7/96) FDM Code 310-EST-1996 (NDA volume 1.005 page 68)].
[Pantoprazole I.V. admixture Compatibility Study" (W-A GTR-33231 submitted in the original NDA volume 1.005 page 79); version 1.1 revised for clarification regarding the light conditions used and was included in volume 2 of this submission.]

FEB - 2 2001

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-988/AZ
Sponsor:	Wyeth-Ayerst PO Box 8299, Philadelphia, PA
Submission:	Response to Approvable Letter
Date Submitted:	January 19, 2001
Drug:	PROTONIX® I.V. for injection (pantoprazole sodium)
Pharmacological Category:	Proton Pump Inhibitor
Proposed Indication:	Short-term Treatment of GERD
Material Submitted/Reviewed:	A Letter, Proposed Packaging and Labeling Changes
Reviewer:	Raymond E. Joseph, M.D.

I. INTRODUCTION

The purpose of this submission was to respond to the requests to (1) modify the container and (2) revise the proposed package insert labeling.

The proposed insert labeling changes will be dealt with at a later date.

In essence, this reviewer agrees with the proposed container that ensures that the drug vials and filters are shipped, delivered to hospital pharmacies, and dispensed together. At the hospital, these two items will be separated; one will be refrigerated and the other will be kept at room temperature. At the time of usage the filter and medication should be reunited. Also, there is agreement with the use of instruction stickers on the I.V. bags to facilitate communication between the hospital pharmacy and patient floor personnel that in-line filters are required during the administration of PROTONIX I.V. for injection.

II. RECOMMENDATIONS

A. On the outside carton where it is stated **contents** (1) change the number (25) instruction stickers to *(30) stickers*. Under (2) in **contents** change to *1 carton of 2 required in-line filters.*

B. On the outside carton where it is written -**"an in-line membrane filter etc."**, change to *the in-line filter provided must be used.*

C. There should be a separate box inside the outer carton for the in-line filters. This box should have the same color, font, pattern and background as the outer carton. The filter box label should read *in-line filters for PROTONIX I.V.*. Also, in this filter bos each individual filter package should have a label attached that reads; *in-line filters for PROTONIX I.V.*

D. The instruction labels in the small medicine-vial box should read: *Filtration required use provided filter*. A copy of this instruction label should be on the outside of the small medicine box. Give (30) instruction labels per (25) vial medicine box.

E. All instruction label fonts should be as large as feasible.

Raymond E. Joseph, M.D.

cc:
NDA 20-988
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-180/RJoseph
HFD-181/CPerry
HFD-180/JChoudary
HFD-180/LZhou
f/t 1/31/01 jgw
N/20988101.0RJ

/s/

Raymond Joseph
2/2/01 10:16:30 AM
MEDICAL OFFICER

Hugo Gallo Torres
2/2/01 11:11:23 AM
MEDICAL OFFICER

Lilia Talarico
2/2/01 11:21:45 AM
MEDICAL OFFICER

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-988
Sponsor:	Wyeth-Ayerst PO Box 8299, Philadelphia, PA 19101
Date Submitted:	October 6, 2000
Drug:	Protonix® I.V. for injection (pantoprazole sodium)
Pharmacological Category:	Proton Pump Inhibitor
Proposed Indication:	Treatment of Erosive Esophagitis
Material Submitted/Reviewed:	Vol. 1 of 1: Oct. 6, 2000 letter from company Hospital survey, summary of feasibility issues associated with proposed kit for I.V. use
Reviewer:	Raymond E. Joseph, M.D., F.A.C.P.

Brief Regulatory History

A new drug application was received July 20, 1998 (NDA 20-988) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Protonix I.V. (pantoprazole sodium) for injection. Protonix I.V. was indicated for short-term gastric acid suppression in gastroesophageal reflex disease patients (GERD) who are unable to take oral medication. The NDA received an approvable action July 20, 1999 to which the sponsor responded on August 31, 1999. At that time the chemistry reviewer found a[ ] Another approvable action was given February 24, 2000. The sponsor responded on May 2, 2000 with suggestions on how to deal with the need for a use of a filter. In the present submission, the sponsor provides additional information on the proposed marketing of this drug.

I. BACKGROUND

In the course of the chemical review of NDA 20-988 for Protonix I.V., the chemistry reviewer, Dr. M. Kowblansky, notified the sponsor concerning particle formation when admixtures of the product are prepared with any of the commonly used diluents, saline, dextrose or lactated Ringer's solution. The sponsor was asked to characterize and attempt to remove or prevent formation of this particulate -- it is a [redacted] Wyeth-Ayerst was unable to remove the precipitate. The agency therefore requested that an in-line filter needs to be used with all commercial containers and diluents.

II. FEASIBILITY ISSUES (sponsor's data)

PROTONIX I.V. is supplied as a lyophilized powder in a 12 mL glass vial, which must be stored under refrigeration. Planned bulk packaging is in cartons containing 25 vials. Alternatively, the agency has suggested individual packaging of a single vial with an in-line filter as a kit. It is the sponsor's assertion that this may be problematic for several reasons:

a) **Storage**

The candidate filters that may be used with PROTONIX I.V. (in their respective sterile packaging) are approximately 3 to 4 times the size of the PROTONIX vial and are recommended to be stored at room temperature. It is anticipated that storage of the bulky individual vial/filter kit will not be practical in hospital pharmacies where refrigerated storage space is generally limited. It is expected that the majority of hospitals would separate the filters (recommended to be stored at room temperature) from the vial (recommended for storage under refrigeration) long before the drug is dispensed for a particular patient.

b) **Vial and filter are used by different health care professionals in different locations in the hospital**

Appropriate reconstitution and administration to PROTONIX I.V. requires the involvement of the hospital pharmacist and the nursing staff on the unit or floor where the drug will eventually be administered. The PROTONIX vial is opened, reconstituted, and admixed by the hospital pharmacist. A computer-generated adhesive label is applied to the I.V. bag containing patient identifiers and formulary information with special instructions for administration, such as "use with an in-line filter," and it is sent to the patient unit or floor. After it is received by the floor or unit nurse, the I.V. bag is attached to the administration set, tubing, and in-line filter, which are usually available on the patient unit or floor.

According to the sponsor, enhancing communication between the pharmacist and the nurse who will administer PROTONIX I.V. will be the most effective method to ensure that the product is administered through an in-line filter as directed.

c) **Hospitals have preferred filters and intravenous administration sets**

Hospitals stock specific in-line filters that are most compatible with their particular brand(s) of I.V. bags, administration sets and tubing. If a particular filter were to be supplied with the PROTONIX I.V. vial, it may not be the hospital's preferred filter for use with the available I.V. tubing and administration sets. Under this circumstance, the Wyeth-Ayerst supplied filter may be discarded.

III. HOSPITAL SURVEY (Additional sponsor's data)

Wyeth-Ayerst performed a hospital survey regarding the use of in line filters.

The data were collected from 46 different institutions; 36 academic centers and 10 community hospitals. All 46 hospitals stock and use filters with a pore size[ ] Many sites stock more than one pore size below[ ]14 different brands). All 46 hospitals have a mechanism in place to provide filters whenever appropriate. In addition:

- 80% of the hospitals stock filters on the patient floor or unit, and the pharmacist applies a computer-generated adhesive label to the I.V. bag.

- 20% stock filters in the pharmacy. These hospitals send a filter from the hospital pharmacy to the floor with the I.V. bag.

- All hospitals surveyed have filters appropriate for use with Protonix I.V. available and procedures in place covering use of parenteral products requiring filtration.

IV. WYETH-AYERST PROPOSAL

The sponsor's proposals for encouraging the use of filters include:

V. REVIEWER'S OVERALL COMMENTS

- Although all of the Wyeth-Ayerst proposals would help somewhat, none can guarantee that the appropriate filters will be used at all times when the medication is given.
- It is possible that the hospital personnel could easily omit the use of the proper filter.
- Co-packaging remains the most likely method to ensure the use of the appropriate filter.

IV. RECOMMENDATIONS FOR REGULATORY ACTION

- It is recommended to continue requiring of the sponsor to co-package. The Agency should insist on this because having the filter and the medicine co-packaged together would increase the chances that a) a filter will be used; and b) the appropriate filter would be used.
- Alternative solutions continue to be discussed with the sponsor.

/S/ 1/3/01

Raymond E. Joseph, M.D.

cc:
NDA 20-988
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-180/RJoseph
HFD-181/CPerry
HFD-180/JChoudary
HFD-180/LZhou
r/d 10/24/00 jgw
f/t 12/29/00 jgw
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