CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-987

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JAN 2 8 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-987 SUBMISSION DATE: 01/07/00

STERILE PANTOPRAZOLE SODIUM TABLET
PROTONIX™
40 MG ENTERIC-COATED TABLET

WYETH-AYERST LABORATORIES
P.O. BOX 8299
PHILADELPHIA, PA 19101-8299 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: RESPONSE ON PROPOSED LABELING

SYNOPSIS/BACKGROUND

This amendment to NDA 20-987 for pantoprazole sodium (Protonix™) 40 mg enteric-coated tablet was submitted by the sponsor on January 7, 2000. Protonix™ is proposed for short-term treatment – 8 weeks) of erosive esophagitis associated with gastroesophageal reflux. In the drug product labeling, it is stated that "for those patients who have not healed after eight weeks of treatment, an additional 8 week course of PROTONIX™ may be considered". The 40 mg strength was selected for marketing in that in clinical studies, it was significantly more efficacious than the 10 and 20 mg strengths but was similar in efficacy to the higher strengths tested (60, 80 and 120 mg). Pantoprazole acts by non-competitive inhibition of the proton pump via covalent binding to the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell.

In this amendment, the sponsor provides responses on the clinical pharmacology labeling changes proposed by the Agency in the review dated November 3, 1999.

REVIEW OF SPONSOR'S RESPONSES ON THE CLINICAL PHARMACOLOGY LABELING COMMENTS

Pharmacokinetics

The initially submitted pharmacokinetics section of the proposed labeling contained the following statement as it relates to normal metabolizers of pantoprazole with normal liver function:

This statement is consistent with the findings of the dose proportionality studies submitted in the original NDA. The sponsor now revises the proposed labeling to eliminate this statement.

In this section, the sponsor replaces ——— the unit of AUC with "μg.h/mL", ——— with "total clearance" and ——— ——— with "volume of distribution".

Recommendation: Since only the 40 mg strength of pantoprazole enteric-coated tablet is proposed for marketing, the sponsor's revision is considered acceptable. The replacement of ——— " with "μg.h/mL" and of ——— with "total clearance" are also acceptable. However, the sponsor's version needs to be further modified by replacing "volume of distribution" with **apparent volume of distribution** (see **Distribution** below).

Distribution

The Agency's version of this section contains the term, "apparent volume of distribution". The sponsor revises this section replacing this term with "volume of distribution".

Comment: The volume referred to in this section is not a true (physiologic) volume. It is a ratio of the administered pantoprazole dose to its initial serum concentration (C_0) to which a volume unit is conveyed by a mathematical circumstance. The Agency considers that it is necessary to distinguish this ratio from a physiologic volume.

Recommendation: It is recommended that the term, "**apparent volume of distribution**" be retained in this section of the proposed labeling.

Metabolism: The Agency's version of this section contains the following statement:

[ ]

The sponsor revises this section replacing ——— with "**from 3.5 to 10.0 hours**" and eliminating ———

Recommendation: The sponsor's revision is acceptable; however, "from" should be replaced with the word, **of** and "had" should be replaced with the word, **have**.

Information for Patients and Dosage and Administration

The Agency's version of this section contains the statement, that pantoprazole enteric coated tablet "should be swallowed whole, ——— with or without food in the stomach". The sponsor revises this section to eliminate the phrase, ———

Comment: There appears to be no established precedence that the phrase, ——— must be used in this case.

Recommendation: The sponsor's revision is considered acceptable.

Precautions

Under **General Precautions**, the Agency stated the precautionary information related to impaired function at two locations (as items 68 and 75 [see the attached Proposed Labeling]). The sponsor revises this section eliminating item 75.

Recommendation: The sponsor's revision is acceptable.

RECOMMENDATION

This amendment to NDA 20-987 for pantoprazole sodium (Protonix™) 40 mg enteric-coated tablet submitted by the sponsor on January 7, 2000 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The proposed drug product labeling needs to be further modified as recommended under **Pharmacokinetics**, **Distribution** and **Metabolism**.

Please convey this Recommendation, as appropriate, to the sponsor.

/S/ 01/28/00

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by Suresh Doddapaneni, Ph.D. /S/ 1/28/00

FT Initialed by Suresh Doddapaneni, Ph.D. /S/ 1/28/00

cc: NDA 20-987, HFD-180, HFD-180 (Walsh), HFD-870 (M. Chen, Huang, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

JAN 27 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-987 SUBMISSION DATE: 12/14/99

STERILE PANTOPRAZOLE SODIUM TABLET
PROTONIX™
40 MG ENTERIC-COATED TABLET

WYETH-AYERST LABORATORIES
P.O. BOX 8299
PHILADELPHIA, PA 19101-8299 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: RESPONSE ON DISSOLUTION COMMENT

SYNOPSIS/BACKGROUND

This amendment to NDA 20-987 for pantoprazole sodium (Protonix™) 40 mg enteric-coated tablet was submitted by the sponsor on December 14, 1999. Protonix™ is proposed for short-term treatment (8 weeks) of erosive esophagitis associated with gastroesophageal reflux. In the drug product labeling, it is stated that "for those patients who have not healed after eight weeks of treatment, an additional 8 week course of PROTONIX™ may be considered". The 40 mg strength was selected for marketing in that in clinical studies, it was significantly more efficacious than the 10 and 20 mg strengths but was similar in efficacy to the higher strengths tested (60, 80 and 120 mg). Pantoprazole acts by non-competitive inhibition of the proton pump via covalent binding to the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell.

In this amendment, the sponsor provides responses on the Protonix™ 40 mg tablet dissolution testing comment contained in the Agency's letter dated November 8, 1999 (see Attachment I).

REVIEW OF SPONSOR'S RESPONSE ON DISSOLUTION TESTING COMMENT

In the original NDA submission, the sponsor's dissolution specification for Protonix™ 40 mg tablet using Apparatus 2 was stated as Q [redacted] at a paddle speed of 100 rpm. However, in the amendment submitted on July 30, 1999, the sponsor provided dissolution data which suggest that a dissolution specification of Q [redacted] at a paddle speed of 75 rpm could be attained. Based on these data, in a letter dated November 8, 1999, the Agency recommended that the drug product dissolution

specification be modified to reflect this new finding (Q_____ at a paddle speed of 75 rpm).

The sponsor states (i) that currently available data do not provide sufficient statistical confidence to justify the dissolution specification changes recommended by the Agency, (ii) that additional drug product batches would be evaluated using both the NDA method and specification (i.e., Q_____ at a paddle speed of 100 rpm) and the Agency proposed specification (i.e., Q_____ at a paddle speed of 75 rpm), (iii) that the data obtained in the dissolution tests proposed in item #ii above would be statistically analyzed "within 6 months post-approval", (iv) that should the results of the statistical analysis proposed in item #iii above warrant it, the dissolution method and specification would be revised to comply with the Agency's request and (v) that should the results of the statistical analysis proposed in item #iii above fail to warrant the changes requested by the Agency, the data collected would be submitted to the Agency along with the rationale as to why the requested changes could not be effected.

The sponsor's response seems reasonable and is, therefore, considered acceptable.

RECOMMENDATION

This amendment to NDA 20-987 for pantoprazole sodium (Protonix™) 40 mg enteric-coated tablet submitted by the sponsor on December 14, 1999 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The sponsor's response on the drug product dissolution issues contained in this amendment seems reasonable and is, therefore, considered acceptable.

Please convey this Recommendation, as appropriate, to the sponsor.

/S/ 01/27/00
David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by Suresh Doddapaneni, Ph.D. /S/ 1/27/00

FT Initialed by Suresh Doddapaneni, Ph.D. /S/ 1/27/00

cc: NDA 20-987, HFD-180, HFD-180 (Walsh), HFD-870 (M. Chen, Huang, Hunt, Doddapaneni and Udo), CDR (Attn: Zom Zadeng).

NDA 20-987 SUBMISSION DATE: 07/30/99

PANTOPRAZOLE SODIUM TABLET
PROTONIX™
40 MG ENTERIC-COATED TABLET

WYETH-AYERST LABORATORIES
P.O. BOX 8299
PHILADELPHIA, PA 19101-8299 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: RESPONSE TO APPROVABLE LETTER

SYNOPSIS/BACKGROUND

This amendment was submitted to NDA 20-987 for pantoprazole sodium (Protonix®) 40 mg enteric-coated tablet by the sponsor on July 30, 1999. Protonix® is proposed for short-term (≤ 8 weeks) treatment of erosive esophagitis associated with gastroesophageal reflux. In the drug product labeling, it is stated that for patients who have not healed after eight weeks of treatment, an additional eight weeks of Protonix® treatment may be considered.

In this amendment the sponsor submits responses to the clinical pharmacology issues that were raised in the approvable letter for Protonix® 40 mg enteric coated tablets.

REVIEW OF RESPONSES ON OVERALL COMMENTS

Comment 1: In the original NDA submission, a paddle rotation speed of 100 rpm was stated in the dissolution specification for Protonix® 400 mg enteric coated tablet. In Comment 1, the sponsor was requested to submit a dissolution profile for a paddle speed of 50-75 rpm.

The sponsor states (i) that USP 23 Chapters <711> and <724) on Dissolution and Drug Release, respectively, do not state specific agitation speeds that should be used for dissolution testing, (ii) that the USP requirement in this regard is that the apparatus be operated at the agitation speed "specified in the individual monograph", (iii) that the rotation speed of 50-75 rpm for Apparatus 2 (paddle) stated in the CDER Guidance for Industry: Dissolution Testing of Immediate Release solid Oral Dosage Forms (August 1997) does not apply to Protonix®, a modified release dosage form, (iv) that in USP 23, Chapter <1088> (pages 1924-1925) which refers to dissolution testing of modified release dosage forms, such as Protonix®, it is stated that higher rotation frequencies (e.g., the paddle speed of 100 rpm) may be more useful, (v) that in the CDER

Guidance for Industry, SUPAC-MR: Modified Release Solid Dosage Forms (September 1997), the recommended paddle rotation speeds stated in the dissolution documentation requirements are 50, 75 and 100 rpm and (vi) that based on the foregoing, the paddle speed of 100 rpm stated in the dissolution specification for Protonix® 400 mg enteric coated tablet is justified.

The sponsor provides dissolution testing results for the pivotal clinical batch (Batch 296440) of Protonix® 40 mg enteric-coated tablet that was performed using Apparatus 2 (paddle) at rotation speeds of 50, 75 and 100 rpm in-house (i.e., at Wyeth Ayerst Research [WAR]) and at Oranienburger Pharmawerk GmbH (OPW), a subsidiary of Byk Gulden Lumberg Chemische Fabrik GmbH (BG), the supplier of Protonix® tablets (see pages 111-115 of Attachment I). At each site, the dissolution specification (Q ———) stated in the original NDA was met at each paddle speed. For the 50 rpm paddle rotation speed, the sponsor states that differences were noted in the WAR and OPW buffer stage dissolution profiles at the early time points which suggested that the dissolution method was less rugged at this paddle speed (as compared to 75 and 100 rpm). The sponsor further states that the paddle rotation speed of 100 rpm is a rigorous test of the enteric coat of Protonix® tablets in acid which ensures that drug release does not occur before the tablet gets to the target drug release site (the duodenum). The sponsor prefers that this paddle speed (100 rpm) be retained in the dissolution specification. Based on the data submitted by the sponsor, the Agency recommends a paddle rotation speed of 75 rpm, with Q ——— (see Overall Comment [page 10]).

Comment 2: In the original NDA, the sponsor stated the acid (resistance) phase of the dissolution test results for Protonix® 40 mg enteric-coated tablet relative to the Agency's requirement of $\leq$10% in 2 h simply as "conforms". In Comment 2, the sponsor was requested to provide the actual drug release data to support the conclusion of conformity.

The sponsor states (i) that the dissolution test for Protonix® 40 mg enteric-coated tablet was performed on the pivotal batch (Batch #296440) using Method —— (ii) that the results of the acid phase dissolution testing was reported in terms of the ultraviolet absorbance value that represented the percentage of drug released, (iii) that for the method used (Method ——— the absorbance limit for a 10% drug release was —— and (iv) that the absorbance values for the dissolution test for Protonix® 40 mg enteric-coated tablet was ——— (see page 120 of attachment I [Table 1]), which justifies a conclusion of conformity with the Agency's requirement of $\leq$10% in 2 h.

The sponsor states that Method ——— has been revised and renamed Method ——— which is capable of quantifying drug release in terms of the percentage of the drug in the dosage form. The sponsor further states that 'future dissolution results will be reported numerically rather than simply [as] "conforms"'. The sponsor's response seems reasonable and is considered acceptable.

REVIEW OF SPONSOR'S RESPONSES ON THE CLINICAL PHARMACOLOGY LABELIBG COMENTS

Pharmacokinetics

Comment: The Agency modified the Pharmacokinetics section of the proposed labeling to include the essential pharmacokinetic information that was submitted to support pantoprazole approval, including the effect of polymorphic metabolism on pantoprazole pharmacokinetics.

The sponsor revises the Agency's version of this section retaining the area under the serum concentration versus time curve (AUC) and peak serum concentration C_{max}. The sponsor moves total clearance (Cl_T) and terminal elimination half-life ($t_{1/2}$) to Metabolism section, stating that [redacted]. The sponsor moves non-steady state apparent volume of distribution (V_d) to Distribution section and excludes the pharmacokinetic information on poor metabolizers of pantoprazole.

The Agency considers that the Pharmacokinetic section of the drug product labeling should contain appropriate pharmacokinetic characteristics of pantoprazole that were submitted to support NDA approval. These should include the compartmental characteristics (if determined) and the pharmacokinetic parameters ($t_{1/2}$, Cl_T, metabolic clearance [Cl_m], renal clearance [Cl_R], V_d, apparent volume of distribution at steady state [V_{ss}], C_{max}, the time to reach the peak concentration [t_{max}], AUC, etc.) as well as the effects of specific factors (polymorphic metabolism, food, etc.) on the kinetics of pantoprazole. The Agency further considers that the use of a pharmacokinetic parameter to substantiate a claim made in another section of a drug product labeling (e.g. the drug is eliminated only by metabolism since its renal clearance equals its total clearance) does not preclude such pharmacokinetic parameter from inclusion in the Pharmacokinetics section of the labeling.

Recommendation: The Agency recommends that the Pharmacokinetics section be modified as follows (the need to state the apparent volume of distribution as 11.0-23.6 L and the total clearance as 7.6-14.0 L/h instead of [redacted] respectively, as proposed by the sponsor, is covered under **Distribution** and **Metabolism** and [see pages 5 and 6]):

> **Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see Metabolism section) with normal liver function receiving an oral dose of the enteric coated 40 mg pantoprazole tablet, the peak concentration (C_{max}) is — ug/mL, the time to reach the peak concentration (t_{max}) is 2.4 h and the total area under the plasma concentration versus time curve (AUC) is 4.8 (ug/mL)h.**

Absorption

Comment: The Agency modified the Absorption section of the proposed labeling to adequately reflect the food effect (increased t_{max}: 5-12 h [secondary to delayed absorption] observed in 8 of 24 fed subjects versus 1-4 h in 16 of 24 fed subjects and 24 of 24 fasted subjects [see page 29 of Attachment II]). The Agency further suggested that delayed onset of drug effect would result from delayed drug absorption.

The sponsor modifies the Agency's version stating that **"administration of pantoprazole with food delays its absorption up to 2 hours"** and eliminating the statement that

Recommendation: (i)

(ii) The statement, that **"administration of pantoprazole with food delays its absorption up to 2 hours"** needs to be revised as follows to reflect more adequately the findings of the food effect study:

> **Administration of pantoprazole with food may delay its absorption up to 2 hours or longer.**

Distribution

Comment (i): The Agency modified the Distribution section of the proposed labeling by replacing pantprazole apparent volume of distribution (V_d) stated by the sponsor L/kg) with the range of values (11.0-23.6 L) determined by the sponsor in three studies

(Byk Gulden Protocols HP018E, HP003 and FHP027E). The Agency further included the main serum protein (albumin) to which pantoprazole is bound.

The sponsor revises the Agency's version stating that "the volume of distribution of pantoprazole is approximately ——— distributing mainly in extracellular fluid".

The Agency feels that the Distribution section of the drug product labeling is intended to contain information primarily on where, in the body, the drug distributes to following administration. This information may then be substantiated using and appropriate pharmacokinetic parameter.

Recommendation (i): The Agency feels that, ideally, the information in this section should be stated as follows:

[ ]

However, the sponsor's version may be accepted provided that "Volume of distribution" is replaced with **apparent volume of distribution** and "about (——— " is replaced with **11.0-23.6 L.**

The Agency agrees with the sponsor that V_d values can be stated in units of L/kg. Therefore, the sponsor may re-analyze the data on the pantoprazole injection concentrate dose of 40 mg (Byk Gulden Protocol FHP027E) and state the V_d range in L/kg if it is so desired.

Justification for replacing ——— " with 11.0-23.6 L: In a study evaluating intravenous ^{14}C-labeled pantoprazole (60 mg) in 6 healthy male subjects (Byk Gulden Protocol FHP018E), the mean value of pantoprazole V_d was 0.152 L/kg (10.6 L in a 70 kg man) which was comparable to the mean unnormalized values of 11.0-12.0 L determined for unlabeled pantoprazole doses of 10, 20, 40 and 80 mg (n=12 per dose group) in Byk Gulden Protocol FHP003. However, in Protocol FHP027E evaluating the 40 mg injection concentrate and the 45.5 and 91 mg doses injection lyophile formulations of pantoprazole (n=12 per dose group), the mean V_d for the 40 mg injection concentrate dose (23.6 L) approximately doubled the values in Byk Gulden Protocols FHP003 and FHP018E.

Based on these data, the Agency considers that substantial study-to-study variability in the values of pantoprazole V_d does exist. The Agency considers that this variability is more appropriately expressed in the drug product labeling by the range of mean values (11.0-23.6 L) obtained in 90 subjects (in three studies) than by the single mean value ———) obtained in 6 subjects (in one of the three studies). Accordingly, the

Agency has modified the Pharmacokinetics section of the labeling to include this range of mean values of the apparent volume of distribution. The Agency considers that the use of the value of the apparent volume of distribution to support pantoprazole distribution mainly in the extracellular fluid would not preclude its inclusion in the Pharmacokinetics section of the labeling.

Metabolism

Comment: The Agency modified the Metabolism section of the proposed labeling (i) by stating the percentage of pantoprazole eliminated by extensive (normal) metabolites in urine as metabolites, (ii) by including information on unidentified metabolites reported in the NDA and (iii) by providing examples of sub-populations that might exhibit polymorphic metabolism of pantoprazole.

The sponsor revises the Agency's version to exclude the minor metabolic pathways and the minor metabolites. The sponsor states that ——— thereby giving the impression that pantoprazole is eliminated only by metabolism. The sponsor also states that ——— and ———)".

Recommendation (i): Regarding the exclusion of pantoprazole minor metabolites and minor metabolic pathways from the drug product labeling, the sponsor's revision may be accepted since pantoprazole metabolites are not known to be pharmacologically active.

(ii) The first paragraph, ——— should be excluded from this section.

(iii) Regarding poor pantoprazole metabolizers, the statement, ———, should be replaced with the following:

> **Although this population of slow pantoprazole metabolizers had elimination half-life values —— hours, they still had minimal accumulation (<23%) with once daily dosing.**

Justification for Recommendation (ii): In the NDA, the sponsor states (i) that 71% of the administered pantoprazole dose is eliminated in urine as metabolites, (ii) that no unchanged pantoprazole is eliminated in urine and (iii) that 18% of the administered pantoprazole dose is eliminated in feces.

The sponsor does not state that no unchanged pantoprazole is eliminated in feces and has not accounted for 11% of the dose (i.e., the difference between the administered dose and the sum of the fractions eliminated in urine and feces). Threfore, the sponsor has not demonstrated that the metabolic clearance of pantoprazole equals its total clearance. Accordingly, the statement, [redacted] ' is misleading and should be eliminated from the labeling.

Justification for Recommendation (iii): The small number of poor metabolizers reported in the NDA was noted in a limited number of studies (≤3 per study). They were identified through pantoprazole half-life, C_{max} and AUC values that were significantly greater than the values in the majority of subjects (extensive metabolizers). In these subjects, the individual subject variability in these pharmacokinetic parameters was rather large. The Agency considers that, in this case, the whole range of values of the pharmacokinetic parameters (or values derived from them) is more informative than a mean value "(mean, [redacted] " or a limitless range (elimination half-life is "greater than [redacted]). The recommended serum accumulation range (≤23%) is based on the serum accumulation of 23% estimated for the longest elimination half-life (10.04 h) observed in the poor metabolizers.

Justification for Replacement of Mean Total Clearance of ' [redacted] **with 7.6-14.0 L/h (see Pharmacokinetics: Recommendation [pages 3-4]):** In a study evaluating intravenous ^{14}C-labeled pantoprazole (60 mg) in 6 healthy male subjects (Byk Gulden Protocol FHP018E), the mean value of pantoprazole total clearance was 0.123 L/h/kg (8.61 L/h in a 70 kg man) which was within the range of the mean unnormalized values of 7.6-9.0 L/h determined for unlabeled pantoprazole doses of 10, 20, 40 and 80 mg (n=12 per dose group) in Byk Gulden Protocol FHP003. However, in Protocol FHP027E evaluating the 40 mg injection concentrate and the 45.5 and 91 mg doses injection lyophile formulations of pantoprazole (n=12 per dose group), the mean total clearance for the 40 mg injection concentrate dose was14.0 L/h.

Based on these data, the Agency considers that substantial study-to-study variability in the values of pantoprazole total clearance does exist. Accordingly, the Agency considers that this variability is more appropriately expressed in the drug product labeling by the range of mean values (7.6-14.0 L/h) obtained in 90 subjects (in three studies) than by the single mean value ([redacted]) obtained in 6 subjects (in one of the three studies). Accordingly, the Agency has modified the Pharmacokinetics section of the labeling to include this range of mean clearance values (see page 4).

The Agency agrees with the sponsor that total clearance can be stated in units of L/h/kg. Therefore, the sponsor may re-analyze the data on the pantoprazole injection concentrate dose of 40 mg (Byk Gulden Protocol FHP027E) and state the total clearance values in L/h/kg if it is so desired.

Elimination

The Agency modified the **Elimination** section of the proposed labeling to specify that pantoprazole elimination was evaluated only in extensive (normal) metabolizers.

The sponsor has revised the **Elimination** section of the proposed labeling to reflect this fact.

Recommendation: The sponsor's revision is considered acceptable.

Hepatic Impairment

The Agency considered the sponsor's statement, [redacted] in the Hepatic Impairment section of the proposed labeling to be inappropriate since eight subjects, categorized by the sponsor as severely hepatically impaired, were evaluated (Protocol FHP045E [see page 34 of attachment II: Fig. 23]). Accordingly, the Agency requested that the statement be replaced with the pharmacokinetic data obtained in this limited number of patients. Furthermore, the Agency suggested that the statement [redacted]

The sponsor revises the Hepatic Impairment section of the proposed labeling to indicate that there is a "potential for modest drug accumulation [redacted]" in patients with severe hepatic impairments receiving pantoprazole once daily, which "needs to be weighed against the potential for reduced acid control" upon dosing pantoprazole "once every other day" in this patient population.

Recommendation: The sponsor's revision is considered acceptable. However, the serum accumulation value, " [redacted] " should be replaced with (≤21%.)

Justification for Replacing [redacted] " with (≤21%): The Agency considers that due to the small number of patients with severe hepatic impairment evaluated (n=8) in Protocol FHP045E, the range of accumulation values would be more informative than a mean value. The accumulation value estimated by the Agency for the longest pantoprazole half-life (9.4 h) observed in the study was 21%.

Drug-drug Interactions

Comment: There was no Drug-drug Interaction section in the proposed labeling submitted in the NDA. Therefore, the Agency created a Drug-drug Interactions section in the proposed labeling from the *in vitro* and *in vivo* drug-drug interaction information provided in the NDA. The increase in digioxin exposure upon co-administration with

pantoprazole, though not statistically significant, was include considering the narrow therapeutic index classification of digoxin.

The sponsor modifies the Drug-drug Interaction section to eliminate the ——— drug-drug interaction information and as well as the information ———————

Recommendation (i): Since adequate information on *in vivo* drug-drug interaction is available, the sponsor's revision to exclude the information on ——— metabolism is considered acceptable.

(ii) The sponsor's revision to exclude ——————————— with co-administered pantoprazole is considered acceptable if the reviewing medical officer considers that ——————————— in patients concomitantly treated with pantoprazole, that are not statistically significant, are also not clinically relevant.

Precautions

The Agency considers that the following should be included in the Precautions section of the drug product labeling:

> **No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole has not been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation (≤21%) when dosed once daily needs to be weighed against the potential for reduced acid control when dosed once every other day in these patients.**

Dosage and Administration

In the Dosage and Administration section of the drug product labeling, ' ——— needs to be replaced with (≤21%). This has been rationalized under Hepatic impairment (see pages 9-10).

OVERALL COMMENT

In this submission, it is stated that the paddle rotation speed of 100 rpm is a rigorous test of the enteric coat of Protonix® tablets in acid which ensures that drug release does not occur before the tablet gets to the intended drug release site and should, therefore, be retained in the dissolution specification. However, the sponsor also states the following (Volume 2 [page 111]):

> "There was no pantoprazole released during the this stage [acid stage of dissolution testing] for any agitation speed tested [50, 75 or 100 rpm] at either Wyeth Ayrest Research (WAR) or Oraneinburger Pharmawerk GmbH (OPW)".

In the submitted buffer stage pantoprazole dissolution testing results (see pages 111-115 of Attachment I), the percentage of drug released in ——, at a paddle rotation speed of 75 rpm, is —— (SD= —— range= —— n=12) for the WAR site and —— (SD= —— range= —— ; n=6) for the OPW site).

Based on these data, the Agency recommends **a paddle speed of 75 rpm, with** Q—————, in the drug product dissolution testing specification.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION

The sponsor's responses on the clinical pharmacology labeling issues raised in the Approvable Letter for NDA 20-987 for pantoprazole sodium (Protonix™) 40 mg enteric coated tablets, submitted by the sponsor on July 30, 1999, have been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. The Clinical Pharmacology section of the proposed drug product Labeling needs to be revised by the sponsor to reflect the recommendations made under the sub-sections of Pharmacokinetics, Absorption, Distribution, Metabolism, Hepatic Impairment, Precautions and Dosage and Administration (pages 3-9) prior to Labeling approval.

Please convey this Recommendation, and the Labeling Comments and Recommendations (pages 3-9), as appropriate, to the sponsor. The Overall Comment (page 10) should be brought to the attention of the reviewing chemist for his/her input and should be conveyed to the sponsor only if he/she deems it appropriate.

/S/ 11/02/99

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by David Lee, Ph.D. 11/02/99

FT Initialed by David Lee, Ph.D. /S/ 11/3/99

cc: NDA 20-987, HFD-180, HFD-180 (Walsh), HFD-870 (M. Chen, Hunt, Lee and Udo), CDR (Attn: Zom Zadeng).

APPEARS THIS WAY
ON ORIGINAL

NDA #20-987

ATTACHMENT I

13 July 1999

PROTONIX® (pantoprazole sodium) 40 mg Delayed-Release Tablets

Biopharmaceutics Comment 1

In assessing the dissolution profile of the drug product, use of USP Apparatus 2 at a rotation speed of 100 rpm is not acceptable. The USP recommended rotation speed with this apparatus is 50-75 rpm. Submit a dissolution profile using the recommended rotation speed.

Response 1

In USP 23 Chapters <711> and <724>, which are the chapters on Dissolution and Drug Release, respectively, it should be noted that in no place in these chapters does the USP state specific agitation speeds that should be used. What the USP does say is to "operate the apparatus at the rate specified in the individual monograph".

The recommendation for use of USP Apparatus 2, the paddle apparatus, at 50 or 75 rpm can be found in the FDA CDER "Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms" (August 1997) under Appendix A: Dissolution Testing Conditions, page A-2. (See Appendix 9.) However, it should be noted that Protonix® tablets are a delayed release formulation. Also, in USP Chapter <1088> "In Vitro and In Vivo Evaluation of Dosage Forms" (USP 23, pages 1924, 1925) it is stated that for modified-release dosage forms (such as Protonix tablets), higher rotation frequencies (e.g., the paddle at 100 rpm) may be more useful. (See Appendix 10.) In "Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms" (September 1997), on pages 6 and 12, the dissolution documentation requirements are given for changes in Components and Composition – Nonrelease Controlling and Release Controlling Excipients, respectively, for delayed release products. (See Appendix 9.) The testing required is 2 hours in 0.1 N HCl followed by testing in USP buffer media with pH of 4.5 – 7.5 at three rotation speeds. The recommended speeds are 50, 75 and 100 rpm for USP Apparatus 2 (paddles). This suggests that the use of 100 rpm for dissolution testing of delayed release products is acceptable.

Dissolution profiles on the pivotal clinical batch (#296440) have been generated at 50, 75, and 100 rpm by Wyeth-Ayerst Research (WAR) and Oranienburger Pharmawerk GmbH (OPW), which is a subsidiary of Byk Gulden Lomberg Chemische Fabrik GmbH (BG) and ——————— They are attached in Tables 1 - 6 and Figures 1 – 2 for your review. (See Appendix 9.)

The dissolution method for Protonix® tablets was developed by Byk Gulden in accordance with USP 23 <724> Method B for Delayed-release (Enteric-coated) Articles. This method, using 100 rpm as the agitation speed, is the method validated by Byk Gulden and transferred to Wyeth-Ayerst Research, where it was subsequently revalidated at 100 rpm. Batch 296440 does pass the current specification of ——— (Q) in ——— at all paddle speeds tested for this study; however, differences between WAR and OPW data at the early time points, when tested using 50 rpm, were observed. Since the method was not validated at this paddle speed, the reason for these differences is not clear. Subtle differences in testing may have a significant effect at the non-validated paddle speed of 50 rpm which are not observed at other paddle speeds, such as the validated 100 rpm. This indicates that the method using 50 rpm is not as rugged as the method at 100 rpm, where such differences are not observed. It is

important to provide a rigorous test of the enteric coat in acid to ensure that the pantoprazole will not be released before it was designed to release. A paddle speed of 100 rpm provides a greater challenge to the enteric coat during the acid stage than either 75 or 50 rpm. For the reasons described above, it is preferred to maintain the current method with a paddle speed of 100 rpm.

Biopharmaceutics Comment 2

For the acid (resistance) phase of Dissolution Testing, results are provided for the 2-hour time point and are stated as "conforms". Provide the actual drug release data from which conformity was concluded.

Response 2

At the time when the pivotal clinical batch 296440 was first tested, method ——— was used. This is the original method that was transferred to Wyeth-Ayerst Research from Byk Gulden, the innovator and supplier of this batch. In this method, the percent of pantoprazole released is not calculated. Rather, the absorbance of the 2-hour dissolution samples is compared to absorbances that had been determined by Byk Gulden which represent 10% and 25% of pantoprazole released. These values represent the acceptance criteria for enteric coated products in the acid stage. The absorbances obtained at Time Zero for Batch 296440 are given in Table 1. (See Appendix 11.) The absorbance limits for 10% and 25% released are ——— respectively. All of the absorbance values are well below —— (with a maximum value of ——— so the results were reported as "conforms".

Method ——— has subsequently been revised so that the percent released during the acid stage can be quantitated accurately, and so that the actual percent released during the acid stage is reported rather than reporting "conforms". The new method number is ———. This method was used for the stability testing of registration batches A97D060, A97D061, and A97D062, packaged in blisters and will be used for testing of market product. Thus, future dissolution results will be reported numerically, rather than simply "conforms." (The initial stability results for the registration batches packaged in blisters are provided in Table 2.) (See Appendix 11.)

Labeling Comment

Revise the dosage form statement to "Delayed-Release Tablets" and the established name to "pantoprazole sodium ———"

Response

At the time of the submission of the original NDA, a United States Adopted Name (USAN) was not available for the drug substance. The USAN has now been assigned and we have revised the appropriate NDA pages (Chemistry, Manufacturing and Controls (CMC) Summary section 3.4.1.1.1 and main NDA text CMC section 4.2.1.1 (Names)) to reflect the new USAN for the drug substance. We are listing the name pantoprazole sodium ——— as a common synonym name. (See Appendix 12) The requested dosage form name has been utilized in the page headers of this submission as well.

5 PAGE(S) REDACTED

12. EFFECT OF FOOD ON PHARMACOKINETICS: The effect of food on the kinetics of oral enteric coated pantoprazole was evaluated in 24 healthy, overnight fasted volunteers (12 males and 12 females) who received a 40 mg dose followed by an additional 8-hour fast and just before a standard breakfast in a crossover fashion (Byk Gulden Protocol #FHP015; GMR-29715). Plots of individual subject serum concentration of pantoprazole versus time are presented in Figs. 21. The mean + SD pharmacokinetic parameters are presented in Table 15. Evidence of equivalence of pantoprazole systemic availability for the two treatments is presented in Table 16.

Fig. 21. Individual Subject Serum Concentration Profiles of Pantoprazole in in Normal Subjects Following a Single Dose of the 40 mg Enteric Coated Tablet (a) Under Fasted Conditions and (b) Just Before Breakfast

Fig. 23. Plots of Mean ± SEM Serum Concentration of Pantoprazole Versus Time in Normal Subjects and in Subjects with Moderate and Sever Hepatic Impairment Following a Single Oral Dose of the 20 mg Enteric Coated Tablet

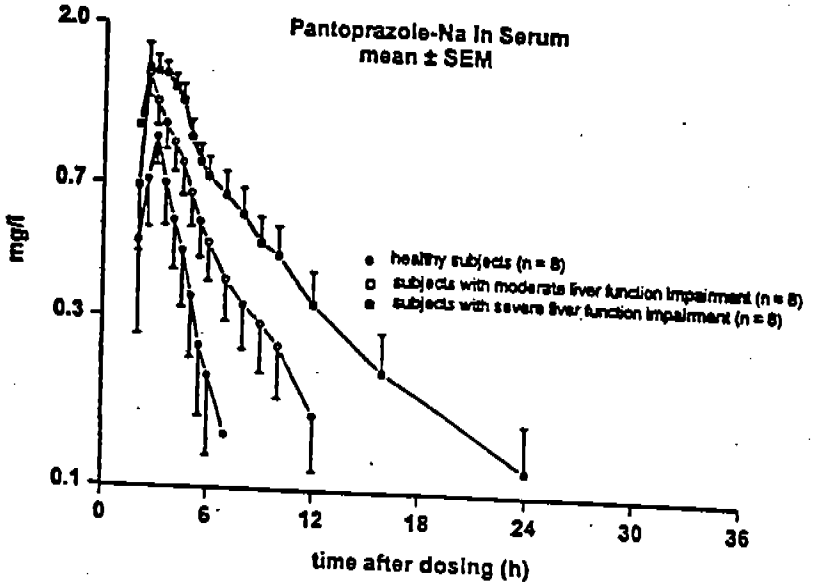
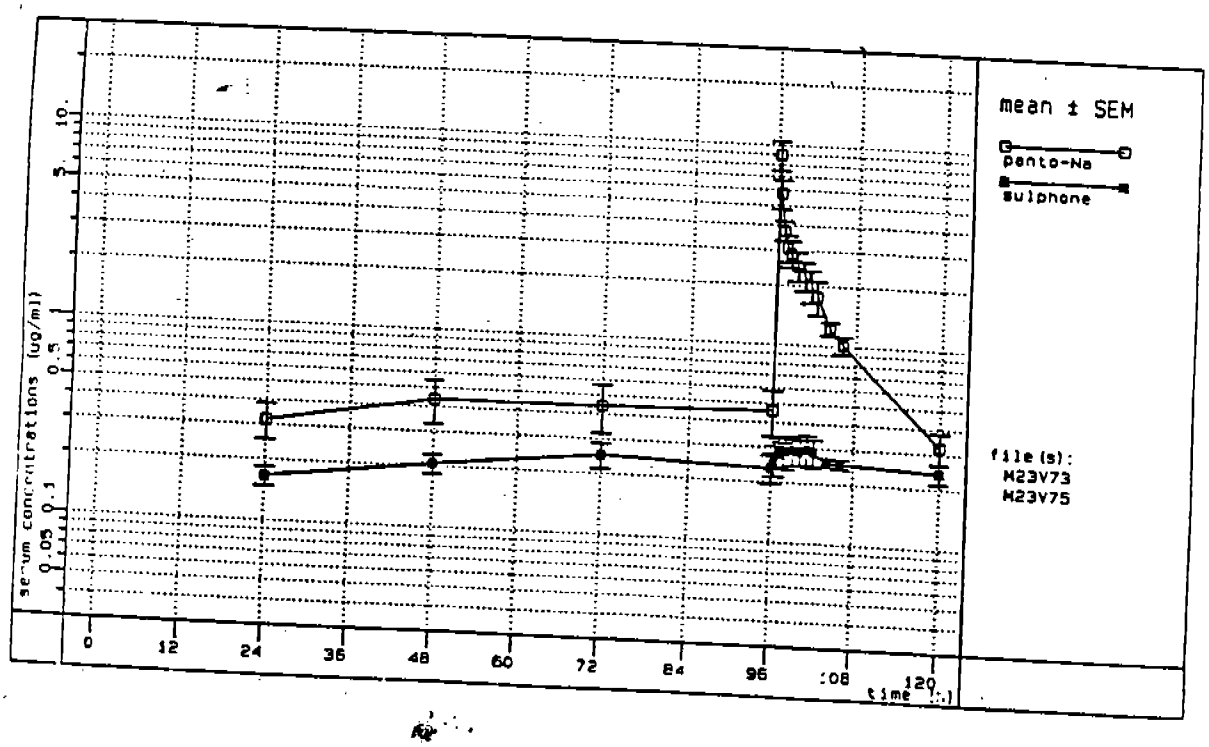


Fig. 24(a). Plots of Mean ± SEM Serum Concentration of Pantoprazole and its Sulfone Metabolite Versus Time in Subjects with Liver Cirrhosis Following a Daily Intravenous Dose of 30 mg for Five Days



NDA 20-987 SUBMISSION DATE: 06/30/98

PANTOPRAZOLE SODIUM TABLET
PROTONIX™
40 MG ENTERIC-COATED TABLET

WYETH-AYERST LABORATORIES
P.O. BOX 8299
PHILADELPHIA, PA 19101-8299 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: ORIGINAL NDA: NEW MOLECULAR ENTITY (NME)

SUBMISSION CODE: 1S

CONTENT

1. SYNOPSIS/BACKGROUND

NDA 20-987 for pantoprazole sodium (Protonix™) 40 mg enteric-coated tablet was submitted by the sponsor on June 30, 1998. Protonix™ is proposed for short-term treatment (~8 weeks) of erosive esophagitis associated with gastroesophageal reflux. In the drug product labeling, it is stated that "for those patients who have not healed after eight weeks of treatment, an additional 8 week course of PROTONIX™ may be considered". The 40 mg strength was selected for marketing in that in clinical studies, it was significantly more efficacious than the 10 and 20 mg strengths but was similar in efficacy to the higher strengths tested (60, 80 and 120 mg). Pantoprazole acts by non-competitive inhibition of the proton pump via covalent binding to the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell.

Based on the information provided in the drug product labeling, benign and malignant neuroendocrine (NE) cell tumors of the gastric fondus and hyperplasia of enterochromaffin-like (ECL) cells were observed in male and female rats treated with Protonix™ doses $\geq$15 mg/kg/day and $\geq$0.5 mg/kg/day, respectively, for 24 months. The labeling recommended dose of Protonix™, 40 mg/day amounts to 0.57 mg/kg/day in a 70 kg individual. The sponsor states that "in 39 patients treated with pantoprazole for 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after four years".

In this NDA, the sponsor submits 53 studies evaluating the pharmacokinetics of pantoprazole following oral and intravenous administration. The intravenous pharmacokinetic studies allowed for a complete pharmacokinetic characterization of this NME. Pantoprazole and its metabolites were quantified by ——— in studies evaluating unlabeled pantoprazole and by counting on a ——— in studies evaluating ^{14}C-labeled pantoprazole. All analytical methods were adequately validated. All concentration values used for characterizing the kinetics of pantoprazole and its metabolites were $\geq$ the limit of quantification. Synthetic metabolites of pantoprazole were generally not available; subsequently, the metabolites were semiquantitatively evaluated (as mg equivalents of the parent drug).

Pantoprazole is metabolized mainly by CYP2C19, and to minor extents by CYPs 3A4, 2C9, 2D6. Its major metabolite is designated as M2 and the other four metabolites are designated as M1, M3, M4 and MX. CYP2C19 exhibits a genetic polymorphism, subsequently, individuals deficient in this isozyme are poor metabolizers of pantoprazole. Pantoprazole is a racemic compound with the center of activity at the sulfur atom. The genetic polymorphism of CYP2C19 is stereo-specific and affects mainly the metabolism of the (+)-enantiomer. The (-)-enantiomer is relatively more toxic than the (+)-enantiomer, however, selective development of the (+)-enantiomer is not recommended since it readily converts to the (-)-enantiomer.

Following oral or intravenous administration, pantoprazole distributes mainly in the extracellular fluid and is 98% bound to serum proteins (mainly albumin). It is rapidly cleared from the serum with a terminal elimination half-life of approximately 1.0 h. Since pantoprazole inhibits the proton pump non-competitively, the inhibition lasts a long time, subsequently, its dosing interval is 24 h. Thus, the dosing interval of pantoprazole is not related to, and cannot be predicted by, its serum half life. Due to the long dosing interval, pantoprazole accumulation does not occur in normal (extensive) metabolizers on multiple dose treatment regimens. Oral or intravenous doses of pantoprazole are eliminated mainly as its metabolites, 71% in urine and 18% in feces. No unmetabolized pantoprazole is eliminated in urine. Orally administered pantoprazole undergoes limited pre-systemic elimination ($\leq$ 15% of the dose).

The absolute bioavailability of the enteric coated 40 mg pantoprazole tablet is 77%. The pantoprazole formulation used in the Phase III clinical studies and the to-be-marketed formulation were similar in composition except for differences in spray patterns of the enteric coating material. These differences were due to the use of a larger scale equipment for the production of the to-be-marketed formulation. The Phase III clinical study enteric coated 40 mg tablet and the to-be-marketd enteric coated 40 mg tablet were bioequivalent. The 20 mg enteric coated tablets (dose =40 mg) used for the later part of the Phase II clinical development and the Phase III clinical study enteric coated 40 mg tablet were also bioequivalent. Pantoprazole dosage adjustment has been recommended for patients with severe hepatic impairment but is not necessary in patients with mild or moderate hepatic impairment, renally impaired patients and elderly patients. Pantoprazole exhibits no gender differences in kinetics and has not been evaluated in pediatric subjects. Food delays the onset of pantoprazole absorption and would, subsequently, delay the onset of its effect. However, overall drug exposure is not affected by food. Clinically relevant interactions of pantoprazole with drugs metabolized CYPs 2C19, 3A4, 2C9 and 2D6 do not occur. Antacids do not affect the absorption of pantoprazole. The slight increases noted in the peak serum concentration and overall exposure of digoxin upon co-administration with pantoprazole are brought to the attention of the sponsor as covered under Labeling Comment 9(b)(iii).

From a pharmacokinetic perspective, the NDA is considered approvable.

II. SUMMARY OF INFORMATION ON , PHARMACOKINETICS, BIOAVAILABILITY, BIOEQUIVALENCE, PHARMACODYNAMICS, ETC.

1. PHARMACOKINETICS:

(a) Intravenous Kinetics of Pantoprazole from Administration of Injection Concentrate Formulation: The pharmacokinetics of pantoprazole was characterized in 12 healthy male subjects receiving single pantoprazole doses of 10, 20, 40 and 80 mg in a cross over fashion by intravenous infusion over 15 min (Byk Gulden Protocol #FHP003; GMR-3007). Plots of mean ± SD serum concentration versus time for each dose level is presented in Fig. 1. The mean±SD pharmacokinetic parameters of pantoprazole obtained in this study are presented in Table 1.

Fig. 1. Mean ± SD Pantoprazole Serum Concentration Versus Time Following Single Intravenous Doses of 10, 20, 40 and 80 mg in 12 Normal Subjects

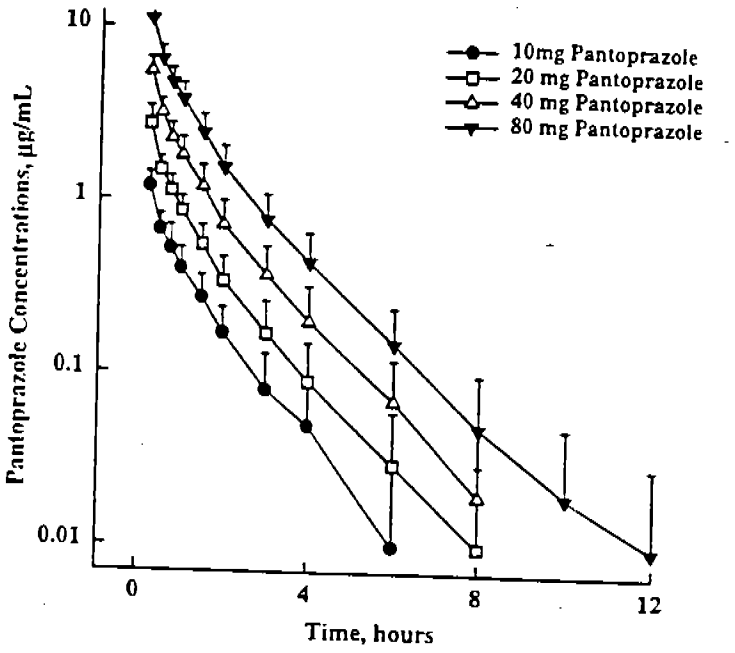


Table 1. Mean + SD Pantoprazole Pharmacokinetic Parameters and Standard Deviation Following Administration of 10, 20, 30 and 40 mg doses by Intravenous Infusion

Dose (mg)	n	C_{max} (mg/L)	t_{max} (h)	AUC ([mg/L]h)	$t_{1/2}$ (h)	Cl_T (L/h)	V_d (L)
10	12	1.19±0.26	0.25	1.2±0.4	0.9±0.2	9.0±2.9	11.7±3.1
20	12	2.74±0.75	0.25	2.6±0.8	1.1±0.4	8.3±2.9	11.5±3.1
40	12	5.52±1.42	0.25	5.4± 1.5	1.0±0.3	7.8±2.7	11.0±1.7
80	12	10.98±2.02	0.25	11.2± 3.0	1.2±0.3	7.6±2.2	12.0±2.1