CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20988

MICROBIOLOGY REVIEW

APR 26 1999

REVIEW FOR HFD-180

OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805
Microbiologist's Review #1 of NDA 20-988

April 20, 1999

A. 1. APPLICATION NUMBER: 20-988

APPLICANT: Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299
(610) 964-5973

2. PRODUCT NAME: Protonix™ I.V.

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Sterile lyophilized pantoprazole sodium (40 mg) in glass vials. For intravenous administration.

4. METHODS OF STERILIZATION:

5. PHARMALOGICAL CATAGORY and/or PRINCIPLE INDICATION: A proton pump inhibitor that suppresses the final step in gastric acid secretion. Proposed indication is for short term gastric acid suppression of gastroesophageal reflux disease (GERD) in patients who are unable to tolerate the oral dosage form.

6. DRUG PRIORITY CLASSIFICATION: 1S

B. 1. DATE OF INITIAL SUBMISSION: July 20, 1998

2. RELATED DOCUMENTS: NDA 20-987(oral pantoprazole)

3. DATE OF CONSULT: July 27, 1998

4. ASSIGNED FOR REVIEW: August 17, 1998

C. REMARKS: The applicant provided an electronic copy (Wyeth-Ayerst server located at the FDA Corporate Blvd facility, Gaithersburg, MD) of the application in PDF format.

D. CONCLUSIONS:

The submission is recommended for approval for microbiology issues concerning, sterility assurance. Specific comments are provided in section "E. REVIEW NOTES".

/S/ 4/20/99

Neal Sweeney, Ph.D.

4/26/99

cc: NDA 20-988
HFD-180/Division File
HFD-180/M.Walsh
HFD-805/Consult File/N. Sweeney

Drafted by: N. Sweeney, April 20, 1999
R/D initialed by P. Cooney, April 20, 1999

Redacted 13

pages of trade

secret and/or

confidential

commercial

information

Manufacturing & Controls

NDA 20-988 SUBMISSION DATE: 08/31/99 NOV - 3

STERILE PANTOPRAZOLE SODIUM
PROTONIX™ I.V. INJECTION

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

TYPE OF SUBMISSION: RESPONSE TO APPROVABLE LETTER

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1. SYNOPSIS/BACKGROUND

This amendment to NDA 20-988 for sterile pantoprazole sodium (Protonix™) I.V. Injection was submitted by the sponsor on August 31, 1999. (Protonix™) I.V. Injection is proposed for short-term treatment (7-10 days) of erosive esophagitis associated with gastroesophageal reflux in patients who cannot take the Protonix™ tablet. The dose recommended in the drug product labeling is 40 mg administered once daily.

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

Pharmacokinetics

Recommendation: The Agency recommends that the Pharmacokinetics section be modified as follows (the need to state the apparent volume of distribution and as 11.0-23.6 L and the total clearance as ___ L/h instead of ___L/kg and ___ L/h/kg,

respectively, as proposed by the sponsor, is covered under **Distribution** and **Metabolism** and [see pages 5 and 6]):

Distribution

Comment: 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 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: 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 ' 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). This 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 a 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 (0.152 L/kg) 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 values of the mean 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 as 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 in poor metabilizers, pantoprazole has an elimination half-life [ ] ___ 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:

[ ]

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). Therefore, the sponsor has not demonstrated that the metabolic clearance of pantoprazole equals its total clearance. Accordingly, the statement, [ ] 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 ($\leq$3 per study). They were identified through pantoprazole half-life, C_{max} and AUC values that were significantly greater than the values in the majority of subjects (extensive metabolizers). In these subjects, the individual subject variability in these pharmacokinetic parameters was rather large. The Agency considers that, in this case, the whole range of values of the pharmacokinetic parameters (or values derived from them) is more informative than a mean value [ ] or a limitless range (elimination half-life is [ ] ___ The recommended serum accumulation range ($\leq$23%) is based on the serum accumulation of 23% estimated for the longest elimination half-life ___ h) observed in the poor metabolizers.

Justification for Replacement of Mean Total Clearance of [redacted] with [redacted] (see Pharmacokinetics: Recommendation [pages 1-2]): 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). This 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 was 14.0 L/h.

Based on these data, the Agency considers that a substantial study-to-study variability in the values of pantoprazole total clearance does exist. The Agency considers that this variability is more appropriately expressed in the drug product labeling by the range of mean values [redacted] obtained in 90 subjects (in three studies) than by the single mean value (0.123 L/kg) 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

Comment: 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 [ ] (i.e., patients with severe hepatic impairment) be replaced by an actual dosing interval (36-48 h estimated by the Agency).

The sponsor revises the Hepatic Impairment section of the proposed labeling stating that there is a [ ] The sponsor retains the statement, [ ].

Recommendation: The sponsor's revision is considered acceptable provided that the following changes are effected:

(i) "(mean %)" should be replaced with **(≤21%).**

(ii) The statement, [ ] should be replaced with the following:

> **The pharmacokinetics of pantoprazole has not yet 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.**

Justification for Replacing "[ ]%)" 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 *in vitro* drug-drug interaction information and as well as the information on the potential of interaction of pantoprazole with digoxin.

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

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

Precautions

The following information should also be included in this section:

Dosage and Administration

(i) In the statement, the **actual type of intravenous administration should be specified. If intravenous infusion, the infusion rate should be stated.**

(ii) The following information should also be included in this section:

RECOMMENDATION

The sponsor's responses on the clinical pharmacology labeling issues raised in the Approvable Letter for NDA 20-988 for sterile pantoprazole sodium (Protonix™) I.V. Injection, submitted by the sponsor on August 31, 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, Distribution, Metabolism, Hepatic Impairment, Precautions and Dosage and Administration (pages 1-7) prior to Labeling approval.

Please convey this Recommendation, and the Labeling Comments and Recommendations (pages 1-7), as appropriate, to the sponsor.

Attachment I is retained in the Office of Clinical Pharmacology and Biopharmaceutics and may be obtained upon request.

/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/ 11/03/99

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

NDA 20-988 SUBMISSION DATE: 07/20/98

STERILE PANTOPRAZOLE SODIUM
PROTONIX™ I.V.

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

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1. SYNOPSIS/BACKGROUND

NDA 20-987 for sterile pantoprazole sodium (Protonix™) I.V. was submitted by the sponsor on July 20, 1998. (Protonix™) I.V. is proposed for short-term treatment 8 weeks) of erosive esophagitis associated with gastroesophageal reflux in patients who cannot take the Protonix™ tablet. The dose recommended in the drug product labeling is 40 mg to be taken once daily. 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 information in the attached review for NDA 20-987 also apply to this NDA except items 1.c-d (Oral Pharmacokinetics), 2 (Bioavailability), 3 (Bioequivalence), 12 (Effect of Food on Pharmacokinetics) 18 (Drug Formulation) and 19 (Dissolution).

From a pharmacokinetic perspective, the NDA is considered approvable.

RECOMMENDATION

NDA 20-988 for sterile pantoprazole sodium (Protonix™) I.V. submitted by the sponsor on July 20, 1998 has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. From a pharmacokinetic perspective, the NDA is considered approvable.

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

/S/ 06/25/99
David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by David Lee, Ph.D. /S/ 6/29/99

FT Initialed by David Lee, Ph.D. /S/ 6/29/99

Clinpharm/Biopharm Briefing: 06/24/99 [Attendees: Selen (HFD-880), Ajayi (HFD-880), Fossler (HFD-870), Suliman (HFD-870), M. Chen (HFD-870), Hunt (HFD-870)].

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