CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20988

ADMINISTRATIVE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: NDA 20-988

Name of Drug: Protonix I.V. (sterile pantoprazole sodium) AUG - 5 1998

Sponsor: Wyeth-Ayerst Laboratories

Material Reviewed

Submission Date: July 20, 1998

Receipt Date: July 20, 1998

Filing Date: **September 18, 1998**

User-fee Goal Date: **July 20, 1999 (12 months)**
May 20, 1999 (10 months)

Proposed Indication: Short-term gastric acid suppression in patients with gastroesophageal reflux disease (GERD) who are unable to take the oral medication.

Other Background Information: The archival copy of this NDA consists of 181 volumes. The entire NDA is also availabel as an electronic review aid via the sponsor's server located at the Corporate Blvd. Building.

Review

PART I: OVERALL FORMATTING[a]

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	x		Vol. 1.001
2. Form FDA 356h (original signature)	x		Vol. 1.001
a.Reference to DMF(s) & Other Applications	x		Vol. 1.001
3. Patent information & certification	x		Vol. 1.001, pages 8-9. Sponsor is requesting 3 years of exclusivity.
4. Debarment certification	x		Vol. 1.001, page 10.

5. Comprehensive Index	x		Vol. 1.001, pages 13-64. A Study Report Location Guide follows on pages 65-90.
6. Pagination	x		Each volume is paginated separately)lower right corner). Each study report is paginated internally (upper right corner).
7. Summary Volume	x		Vol. 1.002
8. Review Volumes	x		All review copies recieved.
9. Labeling (PI, container, & carton labels)	x		
a. unannotated PI	x		Vol. 1.001, pages 169-181.
b. annotated PI	x		Vol. 1.002, pages 1-17.
c. immediate container	x		Vol. 1.001, page 182.
d. carton	x		Vol. 1.001, page 183
e. foreign labeling (English translation)	x		Vol. 1.165. Approved in 5 countries (marketed only in Germany).
10. Foreign Marketing History	x		Vol. 1.002, pages 21-22.
11.Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	x		Archival copy provided on electronic tape. Also provided as part of the electronic review aid.
12.Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	x		Archival copy provided on electronic tape. Also provided as part of the electronic review aid.

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b]

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	x		Vol. 1.002, pages 18-20.
2. Summary of Each Technical Section	x		
a. Chemistry, Manufacturing, & Controls (CMC)	x		Vol. 1.002, pages 23-46.
b. Nonclinical Pharmacology/Toxicology	x		Vol. 1.002, pages 47-93.
c. Human Pharmacokinetic & Bioavailability	x		Vol. 1.002, pages 95-109.
d. Microbiology	x		Vol. 1.002, pages 110-120.
e. Clinical Data & Results of Statistical Analysis	x		Vol. 1.002, pages 121-233.
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	x		Vol. 1.002, pages 234-240.
4. Summary of Safety	x		Vol. 1.002, pages 183-229.
5. Summary of Efficacy	x		Vol. 1.002, pages 165-183.

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c]

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	x		Vol. 1.091, pages 61-65.
2. Controlled Clinical Studies	x		Vol. 160
a. Table of all studies	x		Vol. 1.091, pages 27-58

b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	x		
c. Optional overall summary & evaluation of data from controlled clinical studies		x	
3. Integrated Summary of Efficacy (ISE)	x		Vol. 168
4. Integrated Summary of Safety (ISS)	x		Vols. 169-170
5. Drug Abuse & Overdosage Information	x		Vol. 1.171, pages 341-343.
6. Integrated Summary of Benefits & Risks of the Drug	x		Vol. 1.171, page 344.

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	x		Proposed package insert states that pharmacokinetic information has not been investigated in patients less than 18 years of age and safety and efficacy has not been established in children. The sponsor has no plans to study the drug in the pediatric population at this time.
2. Diskettes	x		All of the information below has been provided via the electronic review aid.
a. Proposed unannotated labeling in MS Word 7.1	x		
b. Stability data in SAS data set format	x		

c. Efficacy data in SAS data set format	x		
d. Biopharmacological information & study summaries in ASCII file format	x		

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Conclusions

No filing issues from an administrative standpoint.

/S/ 8/5/98

Maria R. Walsh, M.S.
Regulatory Health Project Manager

cc:
Original NDA
HFD-180/Div. Files
HFD-180/PM/M.Walsh
HFD-180/L.Talarico
H.Gallo-Torres
J.Choudary
E.Duffy
final: M.Walsh 8/5/98
Filename: 20988808admin.rev.doc

ADMINISTRATIVE REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 31, 2000

FROM: Marie Kowblansky, PhD MK 7/31/00

SUBJECT: Particulates in PROTONIX I.V. Admixtures

TO: John Gibbs, PhD

We are nearing the completion of our review of NDA 20-988 for PROTONIX I.V., a new proton pump inhibitor, submitted by Wyeth-Ayerst. The only outstanding issue is particle formation (exceeding USP limits) when admixtures of the product are prepared with any of the commonly used diluents, saline, dextrose or lactated Ringer's solution. In the original submission the applicant recommended that admixtures be prepared only in polyvinyl chloride containers since particle formation occurred in polyolefin containers. This conclusion was based on limited data. Therefore, at our request they evaluated numerous commercially available containers and administration sets with the conclusion that an in-line filter needs to be used with all commercial containers and diluents. Ample data were provided to demonstrate that the particulates can be removed by filtration without loss in potency and that the filtered solutions remain stable over the recommended 12 hour use period.

At this time we would like to request guidance as to what Center Policy is, or should be, regarding particulate formation in admixtures and the need to filter these solutions prior to infusion. While USP clearly limits the number of particulates permitted in large volume injectable solutions, USP is silent on the issue of filtering to bring these solutions into conformance. Within FDA, there do not appear to be many approved products with this requirement. The applicant has identified only four currently approved products whose admixtures require filtering, Phenytoin, Mannitol, Taxol, and Remicade. (I suspect if there were many more, those also would have been identified.)

As background for your consideration of this problem I would like to summarize the pertinent issues regarding the particulate problem in the current product.

- Based on a variety of experimental techniques[ ]the applicant proposes that the precipitate is a[ ]
- The source of[ ] is from the commercially available diluents which would be used during administration. A critical concentration of[ ]in the diluent is sufficient to cause precititation. (Please note that ppm is well below USP limits for[ ] content in most diluents.) Additional experiments have been conducted to show that removal of [ ]from a diluent solution by eliminates particulate formation in the admixture; conversely, addition of [ ]to a diluent has been shown to increase the amount of precipitate.
- Over 150 combinations of different administration sets, diluents, diluent containers, and manufacturers were studied. In all cases where precipitation was observed, the admixtures were successfully filtered. Although the experimental evidence is convincing that filtration is effective in removing particulates, the experimental design in these experiments does not allow for a clear separation of the variables involved in precipitate formation.

Overall, the combined experimental evidence supports the applicant's conclusion that ___ and pantoprazole are involved in particulate formation. However, based on the experimental design and the

data that were submitted, additional factors are not necessarily excluded. Also, the applicant suggests that the precipitate is composed of with one, two, or three molecules of pantoprazole; the evidence regarding the stoichiometry of the precipitate is not necessarily convincing.

cc: Orig. NDA 20-988
HFD-180/Division File
HFD-180/LTalarico
HFD-180/CSO/CPerry
HFD-820/JGibbs
HFD-180/LZhou
HFD-180/HGallo-Torres
HFD-180/MKowblansky

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 3, 2000 MW 2/3/00

FROM: Maria R. Walsh, M.S., Regulatory Project Manager, HFD-180

SUBJECT: NDA 20-988; Protonix (pantoprazole sodium) for Injection
Reassignment of Chemical Classification Code

TO: NDA 20-988; Protonix (pantoprazole sodium) for Injection

NDA 20-988, Protonix (pantoprazole sodium) for Injection, was submitted on July 20, 1998 and was assigned a Chemical Classification code of Type 1 (New Molecular Entity). However, since NDA 20-987, Protonix (pantoprazole sodium) Delayed-Release Tablets, was approved on February 2, 2000, the Chemical Classification Code for NDA 20-988 will be changed to Type 3 (New formulation of a previously approved active moiety).

cc:
HFD-180/Division file
HFD-180/M.Walsh
HFD-180/L.Zhou
M.Kowblansky

filename: 20988.Feb-2000.memo.doc

NOV 15 2000

MEMORANDUM OF MEETING MINUTES

Meeting Date/Time: September 21, 2000; 11:00 AM – 11:30 AM
September 29, 2000; 11:00 AM – 11:30 AM

Location: Parklawn Building, 6B-45

Application: **NDA 20-988, Protonix® (pantoprazole) I.V. for Injection**

Type of Meeting: Teleconference

Meeting Chair: Dr. Lilia Talarico (9/21/00 conversation)
Dr. Florence Houn (9/29/00 conversation)

Meeting Recorder: Cheryl Perry

September 21, 2000 conversation

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. L. Talarico; Division Director
Dr. H. Gallo-Torres; Medical Team Leader
Ms. K. Johnson; Chief, Project Management Staff
Ms. C. Perry; Regulatory Health Project Manager

Wyeth-Ayerst Laboratories
Mr. James O'Shaughnessy, Associate Director, Worldwide Regulatory Affairs
Ms. Caroline Henessey, Manager, Worldwide Regulatory Affairs

Background:
NDA 20-988, Protonix® (pantoprazole) I.V. for Injection, was approvable 2/24/00 pending resolution of chemistry, manufacturing and controls deficiencies. One of the deficiencies involves a [ ] precipitate that forms both upon reconstitution and when the reconstituted solution is further diluted in mL PVC piggyback solutions prior to administration. The firm submitted a full response to the AE letter on 5/2/00. The Division requested this T-con to notify the firm of their options for addressing this issue. The User Fee Goal date for this Class 2 resubmission is 11/2/00.

Salient points from the conversation included:

1. The Division stated that it remains concerned about the precipitate. In response to a question from us, the firm stated that they are working on the removal of the precipitate from the solution as one of their Phase 4 commitments.

2. The Division stated their position that that Protonix I.V. must be filtered prior to administration, since the compound may be used off-label in patients (newborns, sepsis) where the precipitate could be of clinical significance. In order for the drug to be approved, the firm must do 1 of the following 3 options:

a. reformulate the compound such that a precipitate doesn't form, or

b. package the drug product in a kit with a filter, or

c. if the firm chooses to state in the package insert that a filter should be used, but does not supply the filter, they must conduct a compliance study to see how often the filter is used. Acceptable compliance must be in the _____ % range.

September 29, 2000 conversation

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. Florence Houn, ODEIII Office Director
Dr. S. Aurecchia; Deputy Division Director
Dr. H. Gallo-Torres; Medical Team Leader
Ms. K. Johnson; Chief, Project Management Staff
Ms. C. Perry; Regulatory Health Project Manager

Wyeth-Ayerst Laboratories

Wieslaw Bochenek, M.D., Ph.D.	Senior Director, Clinical Research & Development
Kelly Davis, M.D.	Senior Director, Clinical Research & Development
Caroline Henesey, Ph.D.	Manager, Worldwide Regulatory Affairs
Robyn Karlstadt, M.D.	Senior Director, Medical Affairs
Mr. James O'Shaughnessy	Associate Director, Worldwide Regulatory Affairs
Mr. Robert Zawacki, R.Ph., Esq.	Senior Clinical Pharmacist

The firm requested this teleconference to further discuss the options for addressing the [ ] precipitate.

Salient points from the conversation included:

1. Wyeth-Ayerst stated the following reasons a kit containing the drug product vial and a filter was not a practical remedy.

   a. Pharmacists will be responsible for reconstituting the drug, while nursing personnel will be involved in administration, and the filter may get physically separated from the admixture I.V. piggyback bags in the pharmacy.

   b. The Protonix® I.V. vials of freeze-dried powder for reconstitution must be refrigerated, and storage may be a space problem.

2. Wyeth-Ayerst proposed the following as an alternative to packaging Protonix® I.V. with an approved filter:

   a. Educational materials

   b. Computerized formulary information

   c. Including package sheet of bright label stickers that are specific for Protonix I.V. The label would state the types of filters that are acceptable to use. The

pharmacist would affix the label to the outside of the mL Protonix® I.V. admixture bag.

3. In response to a question, the firm stated their willingness to monitor filter usage post-approval, although additional specifics were not provided.

4. Wyeth-Ayerst stated that in a survey of 40 community hospitals and tertiary care facilities, 100% of these facilities routinely had filters available as a floor stock item. Wyeth-Ayerst's assessment is that the most important component of proper administration is communication between the nurse and the pharmacist.

5. We voiced our skepticism that the firm's proposal would be acceptable, but requested that the firm submit a written proposal for our review.

/S/ 11/15/00
Minutes Preparer: _____
Cheryl Perry, Project Manager

Chair Concurrence: /S/
Lilia Talarico, Division Director

cc: Original NDA 20-988
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/C.Perry
HFD-180/R.Joseph
Drafted by: CP/9-29-00; 10-24-00; 10-29-00
Initialed by: KJ/10-23-00; 10-26-00, 11-14-00
Final: CP/11-15-00
Filename: N20988.T-con.21and 29-Sep-00.doc

MEETING MINUTES

MEMORANDUM OF MEETING MINUTES

Meeting Date: September 9, 1998
Time: 1:00 p.m. - 2:00 p.m.
Location: Conference Room 6B-45, Parklawn Bldg.

Application: NDA 20-988; Protonix I.V. (sterile pantoprazole sodium)

Type of Meeting: 45-day filing meeting

Meeting Chair: Hugo Gallo-Torres, M.D., Ph.D., GI Team Leader

Meeting Recorder: Maria R. Walsh, M.S., Regulatory Project Manager

Attendees:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Hugo Gallo-Torres, M.D., Ph.D., GI Team Leader
Eric Duffy, Ph.D., Chemistry Team Leader
Marie Kowblanski, Ph.D., Chemist
Jasti Choudary, Ph.D., B.V. Sc., Pharmacology Team Leader
Timothy Robison, Ph.D., Pharmacologist

Division of Biometrics III (HFD-720)
A.J. Sankoh, Ph.D., Biostatistics Team Leader
Wen-Jen Chen, Ph.D., Biostatistician

Division of Pharmaceutical Evaluation II (HFD-870)
Alfredo Sancho, Ph.D., Biopharmaceutics Reviewer

Division of Scientific Investigations (HFD-340)
Michael Skelly, Good Laboratory Practices and Bioequivalence Branch

Office of New Drug Chemistry, Microbiology Team (HFD-805)
Neil Sweeney, Ph.D., Microbiologist

Background: Wyeth-Ayerst Laboratories submitted NDA 20-988 for Protonix I.V. (sterile pantoprazole sodium), a proton pump inhibitor, on July 20, 1998, for the following indication: short-term gastric acid suppression in patients with gastroesophageal reflux disease (GERD) who are unable to take the oral medication.

Meeting:

1. **Administrative**

Filing issues: None

Administrative issues/requests: None

2. Chemistry, Manufacturing, and Controls

Filing issues: None

Scientific issues/requests:

A. A categorical exclusion for an environmental assessment was claimed and found acceptable.

B. The proposed drug product is a lyophilized powder to be reconstituted with 10 mL of 0.9% Sodium Chloride and further diluted (admixed) with 100 mL of 5% Dextrose Injection; 0.9% Sodium Chloride; or Lactated Ringer's Injection.

The reviewer will confirm that the appropriate stability data for the reconstituted/admixed solution is included in the application. (Post-meeting note: the appropriate data are provided).

3. Microbiology

Filing issues: None

Scientific issues/requests: None

4. Nonclinical Pharmacology

Filing issues: None

Scientific issues/requests: None

5. Biopharmaceutics

Filing issues: None

Scientific issues/requests: None

6. Clinical/Statistics

Filing Issues: None

Scientific issues/requests:

A discussion ensued about the pivotal study. Study #3001K1-309-US is a two-period study (first period - oral pantoprazole; second period - I.V. pantoprazole) without a washout time between the two periods. Does the effect of the first period carry over to the second period? The analysis includes data on the last day of oral treatment and the first and last day of I.V. treatment. It was decided that these data may be adequate to support the proposed indication with some modification (e.g. "for patients who cannot continue to take the oral medication"). This would imply that patients can switch from the oral formulation to the I.V. formulation but not begin on the I.V. formulation.

Conclusion

NDA 20-988 will be filed on September 18, 1998. A team meeting will be scheduled in December 1998 to discuss the progress of the reviews.

Minutes Preparer: /S/ 9/17/98

Chair Concurrence: /S/ 09/17/98

Attachments/Handouts:

cc: Original NDA 20-988
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/PM/M.Walsh
HFD-180/L.Talarico
H.Gallo-Torres
E.Duffy
M.Kowblanski
J.Choudary
T.Robison
HFD-720/A.Sankoh
W.Chen
HFD-870/D.Lee
A.Sancho

Drafted by: M.Walsh 9/16/98
Initialed by: E.Duffy 9/16/98
A.Sankoh 9/17/98
H.Gallo-Torres 9/17/98
final: M.Walsh 9/17/98
filename: 20988809.min

MEETING MINUTES

MEMORANDUM OF MEETING MINUTES

Meeting Date: March 30, 1998
Time: 1:00 p.m. - 2:30 p.m.
Location: Conference Room P, Parklawn Building

Application: IND [redacted] Pantoprazole Tablets
IND [redacted] Pantoprazole Lyophile

Sponsor: Wyeth-Ayerst Laboratories

Type of Meeting: Pre-NDA - Electronic Regulatory Submission

Meeting Chair: Lilia Talarico, M.D., Division Director

Meeting Recorder: Maria R. Walsh, M.S., Project Manager

FDA Attendees:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Lilia Talarico, M.D., Director
Hugo Gallo-Torres, M.D., Medical Officer
Jasti Choudary, Ph.D., B.V.SC., Pharmacology Team Leader
Eric Duffy, Ph.D., Chemistry Team Leader
Arthur Shaw, Ph.D., Chemistry Reviewer
Maria R. Walsh, M.S., Project Manager

Division of Biometrics (HFD-720)
A.J. Sankoh, Ph.D., Statistics Team Leader
Ferrin Harrison, Ph.D., Statistician

Division of Pharmaceutical Evaluation (HFD-870)
John Hunt, Ph.D., Biopharmaceutics Team Leader
Carol Cronenberger, Ph.D., Biopharmaceutics Reviewer

Office of Drug Evaluation III (HFD-103)
Kaye Fendt, MSPH, Information Specialist

Sponsor Attendees:

Wyeth-Ayerst Research
Mizra Beg, M.D., Vice President, Clinical Research and Development
Wieslaw Bochenek, M.D., Senior Director, Clinical Research and Development
Thomas Brunner, Ph.D.. Director, Applications, Clinical Research and Development
Glenda Casper, Manager. Electronic Publishing, Clinical Research and Development
Lynne DeLorme Sullivan. Ph.D., Director, U.S. Regulatory Affairs

Brian Rantz, Associate Engineer, Technical Services
Marianne Shannon Smith, Principal Information Analyst, Information Management

Meeting Objective: To discuss issues regarding electronic regulatory submissions (ERS) for future NDAs.

Background: The sponsor plans to submit an ERS for each of the following NDAs this year:

Pantoprazole Tablets. Proposed indication: short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease (GERD).

Pantoprazole Lyophile. Proposed indications: short-term treatment of pathological hypersecretory states, i.e. Zollinger-Ellison Syndrome, and short-term use in GERD patients unable to take the oral dosage form.

The sponsor submitted background packages to the respective INDs on March 13, 1998 containing their ERS content proposal and a list of questions to be addressed at this meeting. According to the background packages, each ERS will consist of the entire NDA and the clinical datasets for the pivotal studies. The ERS will be installed on each reviewer's desktop via an external hard disk. NDA text will be presented in the Portable Document Format (PDF) and viewed with Adobe Acrobat Exchange. In addition, each reviewer will be provided with an on-line and a hard copy ERS manual as well as a 2-hour orientation and training session and a 1-800 support telephone number.

Agenda Item 1: Sponsor's presentation/demonstration of the proposed ERS (see attached slides).

Decisions (agreements):

The case report forms (CRFs) and case report tabulations (CRTs) will be provided exclusively in electronic format. Therefore, no volume enumeration will be seen in the table of contents for these items. The archival copy of the CRFs and the CRTs will be installed on the FDA central server by FDA information technology staff. The external hard drive will not contain a copy of the CRFs and CRTs.

A table should be included in the Chemistry, Manufacturing, and Controls section of each NDA which lists the purity profile of each lot used in all the clinical and pharmacology studies. Each lot should be linked to the study or studies in which it was used.

The NDAs should specify if Smith Kline Beecham ever manufactured the drug product used in the clinical studies.

The drug product stability data will be provided in SAS format as part of the ERS and not on diskette. The stability data from Byk Gulden will not be in electronic format.

The data from the animal carcinogenicity studies will be provided on diskette as discussed at the October 15, 1997 pre-NDA meeting.

The efficacy and demography datasets for the statistical reviewer will be provided in SAS Version 5 transport files. Sample SAS codes will be provided.

The possibility of using the sponsor's server (located in the Corporate Blvd. Building) instead of an external hard drive was discussed. It was determined that this issue needs to be discussed further internally by FDA staff.

Unresolved issues: Whether to use an external hard drive or the sponsor's server.

Action Items: The FDA staff will discuss this issue internally and provide feedback to the sponsor as soon as possible.

Agenda Item 2: Will each NDA have the same reviewers? Can the names of the assigned reviewers be provided to Wyeth-Ayerst 4 weeks before the NDA submissions?

Decisions (agreements): Each NDA will probably have the same reviewers but assignment will depend on workload. The names of the reviewers can be provided 4 weeks before the submissions. The planned submission date at this time for both NDAs is June 30, 1998.

Unresolved issues: None.

Action Items: HFD-180 will provide the names of the assigned reviewers to the sponsor 4 weeks before the NDA submissions.

Agenda Item 3: Will each reviewer have a FDA owned PC/workstation with:

- at least 32 megabytes of RAM
- a Pentium 586 processor
- a 21 or 25 inch monitor
- Microsoft Win95 operation system
- the version of Win95 that supports greater than 2 gigabyte files (FAT32)?

Decisions (agreements): Each reviewer has a FDA owned PC/workstation with all the above except a 21 or 25 inch monitor. The current monitor size is 17 inches. The larger

monitors will not be provided by the sponsor. Several 21 or 25 inch monitors will be available from the FDA in the future.

Unresolved issues: None.

Action Items: None.

Agenda Item 4: Will each reviewer have the following software installed prior to our submissions:

- Microsoft Word
- Adobe Acrobat Exchange

Decisions (agreements): Each reviewer has Adobe Acrobat Exchange installed on their PC at present. Microsoft Word will be installed by the FDA in the near future. This software will be available to the medical reviewer before June 1998.

Unresolved issues: None.

Action Items: None.

Agenda Item 5: Wyeth-Ayerst Research will provide each reviewer with an external 5 gigabytes or greater hard drive with a SCSI-2 interface card and cable. The hard drive will be needed to store every item of the NDAs in a PDF format.

Decisions(agreements): The possibility of using the sponsor's server (located in the Corporate Blvd. Building) instead of an external hard drive was discussed above.

Unresolved Issues: Whether to use an external hard drive or the sponsor's server.

Action Items: The FDA staff will discuss this issue internally and provide feedback to the sponsor as soon as possible. The sponsor will work with the FDA's Office of Information technology (OIT) and ODE III staff to test the speed of the sponsor's server.

Agenda Item 6: The FDA will have post-script level 2 printers available for the reviewers to print from the ERS.

Decisions (agreements): The FDA has HPGL and HP4M printers which can probably handle post-script level 2.

Unresolved Issues: Can FDA printers handle post-script level 2?

Action Items: The sponsor will test the FDA's printers for post-script level 2.

Agenda Item 7: All installation will be handled by the computer staff at the FDA, facilitated by Wyeth-Ayerst IT staff and coordinated by Wyeth-Ayerst Regulatory Affairs.

Decisions (agreements): This proposal is acceptable.

Unresolved Issues: None.

Action Items: None.

Agenda Item 8: What is the process or procedure for changing the configuration of FDA PC hardware and software (i.e. adding an external hard drive)?

Decisions (agreements): The sponsor is concerned about the security of the desktop during installation of the external hard drive. This procedure will be coordinated with Mr. Ken Edmunds, Electronic Submissions Coordinator, from FDA's technical support staff.

Unresolved Issues: None.

Action Items: None.

Agenda Item 9: To be consistent with FDA's electronic records signature requirements, Wyeth-Ayerst would like to install the scanned case report forms (CRFs) and case report tabulations (CRTs) on FDA's central server.

Decisions (agreements): The archival copy of the CRFs and CRTs should be installed on the FDA's central server. Additional copies should be installed on the sponsor's server rather than the external hard drive.

Unresolved Issues: None.

Action Items: None.

Agenda Item 10: The CRFs received from Byk Gulden will be scanned in the order in which they are compiled, i.e. in a visit number sequence. The CRFs from Wyeth-Ayerst will be scanned in a file order and then in a chronological order within the file, i.e. all clinical laboratory data together, all AE data together.

Decisions (agreements): This proposal is acceptable.

Unresolved Issues: None.

Action Items: None.

Agenda Item 11: Are there any other experiences with this type of ERS installation that should be discussed to avoid potential obstacles or issues?

Decisions (agreements): Reverse video will not be available from the sponsor. No other issues were discussed.

Unresolved Issues: None.

Action Items: None.

Minutes Preparer: /S/ 4/9/98

Chair Concurrence: /S/ 4-9-98

Attachments/Handouts: Sponsor' slide presentation

Walsh

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 15, 1997
Time: 1:00 p.m. - 3:00 p.m.
Location: Conference Room A, Third Floor, Parklawn Bldg.

Application: IND Pantoprazole I.V.

Type of Meeting: Pre-NDA

Meeting Chair: John Senior, M.D., Medical Officer

Meeting Recorder: Maria R. Walsh, M.S., Project Manager

FDA Attendees:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Lilia Talarico, M.D., Acting Director
John Senior, M.D., Medical Officer
Hugo Gallo-Torres, M.D., Ph.D., Medical Officer
Jasti Choudary, Ph.D., B.V.Sc., Pharmacology Team Leader
Eric Duffy, Ph.D., Chemistry Team Leader
Maria R. Walsh, M.S., Regulatory Project Manager

Division of Pharmaceutical Evaluation (HFD-870)
Lydia Kaus, Ph.D., Biopharmaceutics Team Leader

Division of Biometrics (HFD-720)
A.J. Sankoh, Ph.D., Statistician
Ferrin Harrison, Ph.D., Statistician

External Constituent Attendees:

Wyeth-Ayerst Research
Mizra Beg, M.D., Assistant Vice President, Clinical Research and Development
Wieslaw Bochenek, M.D., Senior Director, Clinical Research and Development
Richard Heaslip, Ph.D., Director, Project Management
Patrick Martin, M.D., Director, Clinical Pharmacology
David Miska, M.D., Associate Director, Clinical Research and Development
Robert Northingham, Ph.D., Associate Director, Clinical Biostatistics
Helena Ryer, Ph.D., Senior Scientific Writer, Clinical Research and Development
Arthur Singer, Ph.D., Principal Statistician, Clinical Biostatistics
Eleanor DeLorme Sullivan, Ph.D., Associate Director, Regulatory Affairs
Vincent Zucal, Coordinator, Regulatory Affairs

Background: IND_____ was submitted on December 10, 1996 to study the use of pantoprazole lyophile for intravenous injection in the control of hypersecretion of acid in patients with Zollinger-Ellison Syndrome (ZES). The Agency met with the sponsor on April 29, 1997 to discuss phase III clinical development plans for the short-term use of pantoprazole I.V. as an alternative dosage form in patients with ZES and other patients who cannot take oral medication. The sponsor subsequently submitted a protocol to the IND on September 4, 1997 to study the short-term use of pantoprazole I.V. as an alternative dosage form in patients with gastroesophageal reflux disease (GERD).

The sponsor requested this pre-NDA meeting to discuss proposed formats for various sections of a future NDA for pantoprazole I.V. A pre-meeting package was submitted to the IND on September 24, 1997. A pre-NDA meeting was held earlier today to discuss proposed formats of a future NDA for pantoprazole tablets.

Meeting Objective:

To obtain Agency comments and concurrence regarding the following:

1. Draft Table of Contents
2. Proposed Format for the Integrated Summary of Effectiveness Data
3. Proposed Format for the Integrated Summary of Safety Information
4. Sample Case Report Form Tabulations: Wyeth-Ayerst
5. Sample Case Report Form Tabulations: Byk Gulden
6. Proposal for the reporting of Byk Gulden safety data
7. Proposed search strategy for developing a bibliography of pantoprazole published literature.
8. Proposal for an Electronic Regulatory Submission

Discussion Points:

1. Introduction

   Dr. DeLorme Sullivan said the target date for the NDA submission is mid-1998 and the proposed indications are: short-term treatment of pathological hypersecretory states, i.e. ZES, and short-term use in GERD patients unable to

take the oral dosage form. She listed the information requested by the Agency to be included in the future NDA (see attached slides # 1 - 3).

2. Efficacy

Dr. Bochenek presented an overview of Study 3001K1-100-US, a pharmacodynamic single dose response study in healthy volunteers (pentagastrin stimulated) and Study 3001K1-304-US, a study of gastric acid suppression in ZES patients, including a description of how the endpoints for each study will be evaluated (see attached slides # 7 - 9). Dr. Martin presented an overview of Study 3001K1-309-US, a study of gastric acid suppression in GERD patients who are switched from oral to IV pantoprazole (see attached slides # 12 - 14). The sponsor also presented a summary of their response to the Agency's letter dated September 18, 1997 regarding the GERD study, which included the modification of the protocol to include a baseline endoscopy.

The qualifications of the primary investigator and the subinvestigators for all seven sites of Study 309 were discussed and the sponsor agreed to submit a curriculum vitae for each of them to the IND.

Dr. Senior reiterated his suggestion for pre- oral pantoprazole measurements of acid secretion rates in Study 309, if pantoprazole IV is to be substituted for other acid suppressive agents. He also advised the sponsor to consider the definition of treatment failure.

A discussion ensued about the appropriate dose and dosing regimen for ZES patients. Drs. Senior and Gallo-Torres recommended that the sponsor provide pertinent information that will guide physicians in selecting the appropriate IV dose for ZES patients especially those who are not well-controlled or who may need a special regimen. The sponsor plans to include in the NDA a description of the individual patients in the ZES studies.

3. Statistical Analyses

Dr. Northington presented an overview of the populations for efficacy analysis, the primary and secondary efficacy endpoints, and the types of statistical analysis to be performed for studies 304 (ZES) and 309 (GERD) (see attached slides # 17 - 24).

A discussion ensued about the statistical analyses. The sponsor clarified that the purpose of the analyses is to reject the hypothesis of non-equivalence between the oral and IV dosage forms. Also, since the studies do not use a wash-out period,

acid measurements are taken after the last oral dose and the last IV dose to help distinguish the effect of the oral preparation from the IV preparation.

4. Safety

Dr. Miska presented an overview of the proposed Integrated Summary of Safety including the main data sets and populations, data listings, adverse events, premature discontinuations, and optic safety for the Wyeth-Ayerst studies (protocols 100, 304, 308, and 309) and the Byk Gulden studies (30 clinical pharmacology studies and two phase III GERD studies) (see attached slides # 26 - 34). The NDA will contain separate data listings for each population in the Wyeth-Ayerst and Byk-Gulden studies.

In response to Dr. Choudary's question, the sponsor said the proposed maximum duration of administration is 7 days. Dr. Senior expressed concern about the potential use of the drug for longer durations and asked the sponsor if they are considering a safety margin study. The sponsor said they plan to pursue additional studies for other indications that will use longer durations. They noted, however, that the NDA will contain Byk-Gulden's safety database which includes two GERD healing studies and a clinical pharmacology study using long-term infusions in healthy subjects.

In response to Dr. Gallo-Torres question regarding the drug interaction study with cisapride, the sponsor said the testing parameters for this study are ECG effects and standard PK and safety testing. He asked the sponsor if there are any studies in which the two drugs are administered concomittanly in patients with a history of cardiac disease. The sponsor will check into this.

5. Other

Dr. Kaus recommended that the sponsor consider addressing the dose-pharmacodynamic data collated in their clinical studies by analyses similar to those used by Sheiner and Mandema and Mandema and Stanski, which have been applied to pain relief and analgesics (a copy of the Mandema and Stanski article, entitled, "Pharmacokinetics and Drug Disposition. Population pharmacodynamic model for ketorolac analgesia," Clinical Pharmacology and Therapeutics, December 1996; 60, pgs. 619-35, was provided to the sponsor).

Dr. Choudary recommended that the NDA for pantoprazole IV contain only the animal studies performed with the IV preparation, with reference to the animal studies performed with the oral preparation contained in the NDA for pantoprazole tablets. He added that the NDA for pantoprazole tablets should

contain both the IV and oral animal studies.

Conclusions

1. The sponsor agreed to submit a curriculum vitae for each subinvestigator involved in Study 309.

2. The sponsor will consider the definition of treatment failure and pre-pantoprazole acid measurements in Study 309.

3. The Division requested that the NDA contain pertinent information that will guide physicians in selecting the appropriate IV dose for ZES patients especially those who are not well-controlled or who may need a special regimen.

4. The sponsor will search for information regarding any drug interaction study in which patients taking cisapride and pantoprazole have a history of cardiac disease.

5. The Division recommended that the sponsor consider addressing the dose-pharmacodynamic data by analyses similar to those used by Sheiner and Mandema and Mandema and Stanski, which have been applied to pain relief and analgesics.

6. The Division requested that the IV NDA contain the animal studies performed with the IV preparation with reference to the animal studies performed with the oral preparation contained in the oral NDA.

Minutes Preparer: |S| 11/10/97

Chair Concurrence: |S| 11-10-97

for |S|

Attachments/Handouts:

WALSH

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 29, 1997
Time: 9:00 a.m. - 11:00 a.m.
Location: Conference Room O, Third Floor, Parklawn Building

Application: IND[ ]
Pantoprazole Lyophile

Sponsor: Wyeth-Ayerst Laboratories

Type of Meeting: Discussion of Clinical Development Plans

Meeting Chair: Hugo Gallo-Torres, M.D., Medical Officer

Meeting Recorder: Maria R. Walsh, M.S., Project Manager

FDA Attendees:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Lilia Talarico, M.D., Acting Director
Hugo Gallo-Torres, M.D., Medical Officer
John Senior, M.D., Medical Officer
Maria Walsh, M.S., Project Manager

Division of Biometrics III (HFD-720)
Mohammad Huque, Ph.D., Team Leader
Ferrin Harrison, Ph.D., Statistician

Division of Pharmaceutical Evaluation II (HFD-870)
Lydia Kaus, Ph.D., Team Leader

External Constituent Attendees and titles:

Wyeth-Ayerst Research
Mizra Beg, M.D., Assistant Vice President, Clinical Research
Wieslaw Bochenek, M.D., Senior Director, Clinical Research
Eleanor DeLorme-Sullivan, Ph.D., Associate Director, Regulatory Affairs
Harold Marder, M.D., Vice President, Clinical Research
Patrick Martin, M.D., Director, Clinical Pharmacology
Philip Mayer, M.D., Senior Director, Clinical Pharmacology
David Miska, M.D., Associate Director, Clinical Research
Jeffrey Paul, Ph.D., Associate Director, Clinical Pharmacology
Arthur Singer, Ph.D., Principal Statistician
Vincent Zucal, Coordinator, Regulatory Affairs

Wyeth-Averst Consultants
Donald O. Castell, M.D., Graduate Hospital, Philadelphia, PA
David Metz, M.D., University of Pennsylvania, Philadelphia, PA
Jeffrey Norton, M.D., Washington University School of Medicine, St. Louis, MO
John H. Walsh, M.D., VA/UCLA, Los Angeles, CA

Background: IND_____ was submitted on December 10, 1996 to study the use of pantoprazole lyophile for intravenous injection (a proton pump inhibitor) in the control of hypersecretion of gastric acid in patients with Zollinger-Ellison Syndrome (ZES). The sponsor requested this meeting to discuss the proposed phase III clinical development plans for the treatment of patients with ZES and for patients who cannot take oral medication. A pre-meeting package was submitted to the IND on March 18, 1997.

Meeting Objectives:

1. Obtain the Agency's concurrence on the clinical development plan for the treatment of patients with ZES.

2. Obtain the Agency's input on the clinical development plan for patients who cannot take oral medications.

Discussion Points (bullet format):

1. Pharmacokinetic Data

   Dr. Mayer presented an overview of the pharmacokinetics (PK), drug interaction, and formulation data for I.V. pantoprazole and a description of the phase I safety and pharmacokinetic studies conducted by Byk Gulden (see attached slides).

   During the presentation of the three different I.V. formulations, Dr. Senior inquired about the pH of the final solution to be infused and the incidence of thrombophlebitis in the clinical studies. Dr. Gallo-Torres also pointed out the possibility of altering the patient's serum pH if the pH of the final solution is high. The sponsor agreed to provide information concerning the pH of the final solution in the NDA as well as the safety data for all three I.V. formulations.

   A discussion ensued about the enantiomers and metabolites of pantoprazole. Dr. Kaus said the relative clearances of the enantiomers following I.V. administration of each of the I.V. formulations versus oral administration should be provided in the NDA as well as information about the activity of the enantiomers and the major metabolites. Dr. Kaus also said that the preclinical and clinical PK data, including protein binding, should be provided in the NDA.

2. Safety and Efficacy Data

Dr. Miska presented an overview of the safety and efficacy data of I.V. pantoprazole from the acid secretion/pH studies [short-term and long-term infusion studies and gastroesophageal reflux disease (GERD) healing studies] conducted by Byk Gulkden (see attached slides). The sponsor concluded that I.V. and oral dosing appear to be equivalent, that pantoprazole I.V. is well tolerated, and that the safety profile of the I.V. and oral formulations are similar.

Dr. Gallo-Torres inquired about nine cases of blurred vision observed in a drug interaction study with I.V. pantoprazole. The sponsor said that blurred vision was considered secondary to hypoglycemia in seven of the nine patients in that study. In addition, the sponsor said two patients in another study experienced blurred vision but it did not recur upon rechallenge. A discussion ensued about 19 cases of visual disturbances in Germany with both the I.V. and oral dosage forms of omeprazole (another proton pump inhibitor). The sponsor said that the visual events occurred in seriously ill patients and a causal relationship to the drug has not been established. Dr. Gallo-Torres pointed out that the labeling for lansoprazole (another proton pump inhibitor) describes the occurrence of retinal atrophy in rats. Because of a potential relationship between visual disturbances and the use of proton pump inhibitors, Dr. Gallo-Torres said the NDA should contain a full discussion of this safety issue, including all available preclinical and clinical safety data regarding eye findings for both the I.V. and oral dosage forms of pantoprazole as well a summary of all the available safety data regarding reports of visual disturbances with the I.V. omeprazole.

3. Ongoing Pharmacodynamic Study

Dr. Martin presented an overview of the ongoing pharmacodynamic study, submitted in IND ____ , Protocol No. 3001K1-100-US, entitled, "A Dose-Ranging Study of Pentagastrin-Induced Gastric Acid Secretion Inhibition by Intravenous Pantoprazole" (see attached slides). The sponsor states that the objective of this study is to assess the magnitude and time course of inhibition of pentagastrin stimulated gastric acid production in order to identify an appropriate I.V. dose and dose regimen for use in ZES patients.

In response to Dr. Senior's question, Dr. Walsh clarified that the cut-off level of acid production for a hyporesponder is 20 mEq/hr. In response to Dr. Gallo-Torres' question, Dr. Walsh explained that the gastric acid output measurement is more precise than the pH measurement because the pH tends to remain at the same level until gastric acid production is abolished. Dr. Senior questioned whether an appropriate dosing regimen might be 40 mg b.i.d. rather

than 80 mg qd. Dr. Walsh said that clinical data indicates that twice daily dosing is more effective in controlling symptoms in ZES patients, however, these two dosing regimens are not being compared in this study.

4. Proposed Phase III Clinical Development Plan

A. Zollinger-Ellison Syndrome

Dr. Bochenek presented the sponsor's proposed study design to evaluate the use of IV pantoprazole in ZES patients, Protocol No. 3001K1-304, entitled, "A Pivotal Efficacy Study of Inhibition of Gastric Acid Secretion By Intravenous Pantoprazole In Patients with Zollinger-Ellison Syndrome With or Without Multiple Neoplasia Type-1 Syndrome" (see attached slides). He noted that his presentation differs from the proposed study design presented in the pre-meeting package. Twelve ZES patients will receive IV pantoprazole for 6 days. The starting dose is 80 mg b.i.d. with increase to 120 mg b.i.d. if gastric acid output is $\geq$ 10 mEq/hr during the first 72 hours. Efficacy endpoints are suppression of gastric acid output to $<$ 10 mEq/hr ($<$ 5mEq/hr in patients with a partial gastrectomy) and control of gastric acid output for at least 24 hours. Dr. Gallo-Torres advised the sponsor to clearly specify the conditions of use in ZES patients.

In response to Dr. Gallo-Torres' question about the safety of the 120 mg b.i.d. dose, Dr. Bochenek replied that a 240 mg bolus dose was administered to fifteen patients in a German study sponsored by Byk Gulden with no adverse effects.

In response to Dr. Gallo-Torres' question about the type of ZES patients to be studied, the sponsor said the patients will be either newly diagnosed or unstable on their current treatment. Dr. Gallo-Torres pointed out that studies with oral omeprazole and oral lansoprazole included 136 patients and 57 patients, respectively and he questioned the small number of patients to be studied with I.V. pantoprazole. The sponsor explained that enrolling newly diagnosed patients is difficult because of the low incidence of the disease and diagnosed patients are frequently enrolled in studies with other proton pump inhibitors.

In response to the sponsor's questions, the Agency concurred that the proposed study (Protocol 304) in ZES patients may be initiated while the PD study (Protocol 100) in healthy volunteers is ongoing and that the proposed study design (Protocol 304) in ZES patients is acceptable. Regarding the sponsor's question about whether these two studies will be sufficient to support the filing of an NDA for pantoprazole lyophile in patients with ZES, Drs. Gallo-Torres and Senior advised the sponsor of the Agency's position that one study in the

target patient population may be sufficient if that study is well-designed and the results are highly compelling. Dr. Gallo-Torres also commented that historical comparators can be problematic. It was recommended that the sponsor consider conducting a second study switching well-controlled ZES patients from their current oral medication to I.V. pantoprazole with similar efficacy endpoints as the proposed study above.

B. Patients Who Cannot Take Oral Medication

Dr. Martin presented the sponsor's proposed clinical development plan to evaluate the use of I.V. pantoprazole in those patients who require suppression of gastric acid and cannot take oral medication (see attached slides). The plan includes the short-term use (up to 7 days) of I.V. pantoprazole as an alternative to the oral dosage form. The clinical endpoint will be based on the pharmacodynamic assessment of gastric acid suppression and the clinical studies will focus on creating a dose-response between the I.V. and oral dosage forms with respect to the gastric acid suppression profile. The sponsor proposes to amend the ongoing PD study (Protocol 100) in healthy volunteers by adding three dose groups: a placebo group, a single dose level of the oral dosage form, and a single dose level of famotidine. The sponsor also proposes to conduct a second PD study (Protocol No. 3001K1-101-US) in healthy volunteers comparing three dose levels of both the oral and intravenous dosage forms.

Dr. Gallo-Torres noted that intravenous gastric acid suppressant drugs are currently being used to treat a variety of conditions including upper gastrointestinal bleeding, stress ulcers, and pneumonitis. In light of this, he asked the sponsor to specify the clinical conditions for the use of I.V. pantoprazole in patients who cannot take oral medication. The sponsor replied that the plan is to establish a substitutable I.V. dose for use in patients who could be given oral pantoprazole but cannot take oral medications. Dr. Gallo-Torres asked the sponsor to define the intended patient population further. The sponsor clarified that the use of I.V. pantoprazole would be limited to whatever indications for which the oral dosage form becomes approved. Since the oral dosage form is currently being studied in GERD, the sponsor said the initial patient population for I.V. use would be patients with GERD who cannot take the oral dosage form.

Dr. Gallo-Torres said that the data obtained in the proposed studies (amended Protocol 100 and Protocol 101) using healthy volunteers may not be extrapolated to sick patients with active disease. Drs. Gallo-Torres and Senior recommended a placebo-controlled switch study in GERD patients. Dr. Gallo-Torres suggested that patients from the ongoing oral GERD studies could be switched to one of two intravenous dose levels for a short period of time. The

sponsor agreed to conduct a study in GERD patients.

In response to the sponsor's questions, the Agency concurred that inhibition of gastric acid secretion is an acceptable endpoint for the proposed studies, including the recommended study in GERD patients. The Agency also concluded that the proposed studies, including the recommended study in GERD patients, are sufficient to support the filing of a NDA for the use of pantoprazole lyphophile in GERD patients who cannot take the oral dosage form. Dr. Gallo-Torres clarified that approval of the oral dosage form for GERD is required before the above indication may be approved. Dr. Talarico said that additional safety data will be required if treatment duration is anticipated to be longer than 7 days.

Conclusions

1. The following information should be provided in the NDA:

   A. Information on the pH of the final I.V. formulation as well as the available safety data for all three I.V. formulations.

   B. Comparative data on the relative clearances of the enantiomers following I.V. administration of each of the I.V. formulations versus oral administration.

   C. Information about the activity of the enantiomers and the major metabolites.

   D. Comparative preclinical and clinical PK data, including protein binding.

   E. A full discussion of the safety information concerning the eye including all available clinical and preclinical safety data for both the I.V. and oral dosage forms as well a summary of the available safety data regarding the reports of visual disturbances with I.V. omeprazole.

   F. Additional clinical safety data if treatment duration is anticipated to be longer than than 7 days.

2. Regarding the clinical development plan in ZES:

   A. The PD study in healthy volunteers (Protocol 100) and the proposed study in ZES patients (Protocol 304) may be adequate to support the approval of a NDA provided the efficacy results of Protocol 304 are highly compelling.

   B. A second study switching well-controlled ZES patients from their current oral medication to I.V. pantoprazole with similar efficacy endpoints as Protocol 304

is recommended and will be needed for the approval of a NDA if Protocol 304 does not produce highly compelling efficacy results.

C. The proposed study design, including endpoints, in ZES patients (Protocol 304) is acceptable.

D. The proposal to initiate the proposed study in ZES patients (Protocol 304) while the PD study in healthy volunteers (Protocol 100) is ongoing is acceptable.

3. Regarding the clinical development plan in patients who cannot take oral medications:

A. Data obtained in the proposed studies (amended Protocol 100 and Protocol 101) in healthy volunteers may not be extrapolated to sick patients with active disease. Therefore, a placebo-controlled switch study in GERD patients is recommended.

B. The Agency suggested that patients in the ongoing oral GERD studies could serve as a study population for the recommended placebo-controlled switch GERD study. Two dosage levels of I.V. pantoprazole should be studied.

C. The Agency concurred that inhibition of gastric acid secretion is an acceptable endpoint for the proposed studies (amended Protocol 100 and Protocol 101) as well as the recommended placebo-controlled switch study in GERD patients.

D. Approval of the oral dosage form for GERD is required before an indication for use of I.V. pantoprazole in GERD patients who cannot take oral medications may be approved.

Minutes Preparer: /S/ 6/12/97

Chair Concurrence: /S/ 6/12/97

Attachments: Slide presentation

/S/ 06/12/97

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20988	**Trade Name:**	PROTONIX IV (PANTOPRAZOLE SODIUM STERILE
Supplement Number:		**Generic Name:**	PANTOPRAZOLE SODIUM STERILE
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	AE	**Proposed Indication:**	Short-term gastric acid suppression in GERD patients who are unable to take oral medication

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy Inadequate for ALL pediatric age groups
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
This application was AE on July 20, 1999. A full response to the AE letter was submitted on August 31, 1999. Another AE action will be taken by March 1, 2000. A PPSR was submitted on June 7, 1999. An inadequate letter was issued on November 9, 1999. A revised PPSR was submitted on January 31, 2000 and is under review.

Pediatric studies will be deferred in the AP letter.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MARIA WALSH

S

Signature

2/22/00

Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20988	**Trade Name:**	PROTONIX IV (PANTOPRAZOLE SODIUM STERILE
Supplement Number:		**Generic Name:**	PANTOPRAZOLE SODIUM STERILE
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	AE	**Proposed Indication:**	Short-term gastric acid suppression in GERD patients who are unable to take oral medication

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?
____NeoNates (0-30 Days)____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MARIA WALSH

/S/ _____ 6/24/99

Signature Date

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-988 MAR 22 2001

Name of Drug: PROTONIX® I.V. (pantoprazole sodium) for Injection

Sponsor: Wyeth-Ayerst Laboratories

Material Reviewed

Submission Dates: January 19, February 8, 14, 21, 22, March 15, and 16, 2001

Receipt Date: January 22, February 8, 14, 23, March 16, and 19, 2001 respectively

Background:

NDA 20-988, Protonix I.V. (pantoprazole sodium) for Injection, submitted January 19, 2001, provides for the following indication: "PROTONIX I.V. 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) Delayed-Release Tablets. Safety and efficacy of PROTONIX I.V. for Injection as an initial treatment for GERD have not been demonstrated."

The January 19, 2001 submission provides for revised, draft package insert, immediate container label, and carton labels in response to a November 2, 2000 approvable letter. The February 8, 14, 23, March 16, and 19, 2001 submissions provided commitments to carton labeling changes requested by the Agency.

Review

The submitted draft package insert labeling, identified as "08-Jan-01" was compared to the labeling submitted May 2, June 23, and September 8, 2000 (see Consumer Safety Officer Review dated November 17, 2000) and the revisions requested in the November 2, 2000 approvable letter. The package insert texts are identical except for the following (text that is <u>underlined</u> indicates wording that has been added; ~~strikethrough~~ indicates wording that has been deleted):

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Draft Labeling

CONCLUSIONS

An **APPROVAL** letter will be issued.

A. PACKAGE INSERT

In response to numerous negotiations between the Division and the sponsor, the sponsor submitted revised draft package insert text via facsimile on March 21, 2001. Further discussions with the firm ensued. The text of the package insert as agreed upon by the sponsor and the Division is appended to this review.

B. VIAL (IMMEDIATE CONTAINER) LABEL AND CARTONS

In response to communications between the Division and the sponsor on March 12 and 13, 2001, the sponsor submitted revised color mock-up copies of the immediate container label and cartons on March 15, 2001. The submitted color mock-ups were reviewed by the Division and are ACCEPTABLE.

Cheryl Perry
Regulatory Health Project Manager

Lilia Talarico, M.D.
Division Director

/s/

Cheryl Perry
3/22/01 02:24:29 PM
CSO

Lilia Talarico
3/22/01 02:55:34 PM
MEDICAL OFFICER

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

NOV 1 7 2000

Finalized after Nov 02, 2000 AE because Kati Johnson was unable to review draft

Application Number: NDA 20-988

Name of Drug: PROTONIX® I.V. (pantoprazole sodium) for Injection

Sponsor: Wyeth-Ayerst Laboratories

Material Reviewed

Submission Dates: May 2, 2000 – Draft package insert (P.I.) labeling submitted in response to the February 24, 2000 approvable (AE) letter. This labeling contained a different indication than that in the (AE) letter.

June 23, 2000 – Revised P.I. labeling which included the indication contained in the February 24, 2000 (AE) letter.

September 8, 2000 – Diskette of June 23, 2000 proposed P.I. labeling.

Receipt Dates: May 2, June 26, and September 11, 2000, respectively

Background:

NDA 20-988, PROTONIX® I.V. (pantoprazole sodium) for Injection, a proton pump inhibitor, was submitted July 20, 1998 for short-term treatment of gastric acid suppression in GERD patients unable to take oral Protonix. The application was AE on July 20, 1999 for the following 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) Delayed-Release Tablets. The AE letter stated the Chemistry, Manufacturing, and Controls (CMC) and labeling deficiencies that needed to be adequately addressed for approval. The application was AE again on February 24, 2000 pending resolution of CMC and labeling deficiencies. The firm submitted draft labeling on May 2, 2000; and revised draft labeling on June 23, 2000. On September 8, 2000, the firm submitted a diskette containing a side-by-side comparison of our February 24, 2000 AE labeling to their June 23, 2000 revised draft P.I. labeling. According to the CMC Review #6 (September 14, 2000), deficiencies remain involving the formation of a _____ precipitate and the _____ specification.

The firm's container and carton labels, submitted August 31, 1999, were found acceptable in CMC Review #3 (dated December 14, 1999). However, the AE letter that will be issued will notify the firm that Therefore, the carton and container labels may be revised in their response to this AE letter. This review is limited to the P.I. only.

Review

The submitted P.I. labeling was compared to the labeling enclosed in the February 24, 2000 approvable letter and the following revisions have been made. Only those sections that have been revised are included. For the sections not included, the firm has revised the labeling as requested. Text that is underlined indicates that wording has been added; ~~strikethrough~~ indicates wording that has been deleted.

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Draft Labeling

Cheryl Perry
Regulatory Health Project Manager

Lilia Talarico, M.D.
Division Director

cc:
Archival NDA 20-988
HFD-180/Div. Files
HFD-180/C.Perry
HFD-180/L.Talarico

Draft: CP/November 1, 2000
R/d Initials: KJ/November 9, 2000
Final: CP/November 16, 2000
Filename: N20988.CSO-labrev.16-Nov-00.doc

CSO REVIEW

/s/

Cheryl Perry
11/17/00 10:08:10 AM
CSO

Review Cycle (2)

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Draft Labeling

Review Cycle (4)

Submitted: 19-Jan-01

FDA Comment
In addition, it will be necessary for you to submit draft labeling for the package insert (PI) identical in content to that submitted on June 23, 2000, revised as follows:

1. The following statement in the **DESCRIPTION** section should be deleted:

Response
We concur on the deletion of this sentence. The labeling for the package insert, updated to address all of the DGCDP's recommendations, is provided in Attachment B-1. Added text is underlined and deleted text is in ~~strikethrough~~.

FDA Comment
2. The last sentence in the **CLINICAL PHARMACOLOGY**, ***Special Populations***, *Hepatic Impairment* subsection should be modified to include the underlined text. The sentence should read, '

Response
We concur that it is appropriate to include the text as recommended. To maintain consistency throughout the document we have also modified the similar statements in the **PRECAUTIONS, General** subsection as requested in recommendation #5a and the last sentence in the **DOSAGE AND ADMINISTRATION** section.

FDA Comment

3. The **CLINICAL PHARMACOLOGY, Pharmacodynamics,** *Antisecretory Activity* subsection should be revised to delete the word [redacted] in the third sentence. The sentence should state, [redacted]

Response

We agree to modify the referenced sentence. The standard dose of 6.0 µg/kg subcutaneous bolus will elicit a maximal gastric acid output (MAO) of 20 to 40 mEq/hr. The regimen used in Study No. 3001K1-100-US of 1.0 µg/kg/hr was chosen because it produces a near maximal acid output that is sustainable for 24 hours. The literature provides evidence that healthy volunteers given 0.6 µg/kg/hour will give a 80% maximal gastric secretory response in 80% of the subjects. (A copy of each of the below articles is provided in Attachment B-2.) Thus, we have revised the referenced sentence to reflect this information.

Mason MC, Giles GR, Clark CG. Continuous intravenous pentagastrin as a stimulant of maximal acid secretion. Gut 1969; 10:34-8.

Wormsley KG, Mahoney MP, Ng M. Effects of a gastrin-like pentapeptide on stomach and pancreas. Lancet 1966; 1:1993-6.

Chin TWF, MacLeod SM, Mahon WA. Absence of tachyphylaxis in gastric acid secretion during pentagastrin infusion. J. Clin Pharmacol 1986; 26: 281-5.

FDA Comment

4. The **Clinical Studies** section should be revised as follows:

   a. The following sentence should contain the underlined text. The statement should read,

   b. The table entitled, "Antisecretory Effects... of PROTONIX I.V. for Injection and the 40 mg Oral PROTONIX in GERD Patients" should be retained as requested in the February 24, 2000 approvable letter, or a justification provided for the requested revisions.

Response

We agree to include the text suggested in recommendation #4a. However, to reflect the actual design of this clinical study, we suggest to replace ' ____ ' with "10 days". We also agree to retain the table entitled, "Antisecretory Effects (mEq/h) of 40 mg PROTONIX I.V. for Injection and 40 mg Oral PROTONIX in GERD Patients" as suggested in the February 24, 2000 approvable letter. We have updated the table to correct the mean basal acid output value for the PROTONIX® I.V. for Injection group to 0.53, which was erroneously reported as ____ We feel that the mean basal acid output data on the first day of intravenous therapy, which was measured at 48 hours after the last oral dose, is clinically important for prescribing physicians. Therefore, we propose to add a description of this data in the second paragraph in the **Clinical Studies** section.

FDA Comment

5. The **General** subsection of the **PRECAUTIONS** section should be revised as follows:
   a. The last sentence in the second paragraph should be revised to be consistent with the wording specified above in recommendation #2.

   b. The statement pertaining to when treatment with the injection should be discontinued should remain as requested in the February 24, 2000 approvable letter. The specific statement should read, "Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets."

Response

We concur with recommendation 5a. Please see our response to recommendation #2. We also concur with recommendation 5b. We have updated the labeling in this subsection and the similar text in the fourth paragraph of the **DOSAGE AND ADMINISTRATION** section.

FDA Comment

6. The **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection of the **PRECAUTIONS** section should be revised. The description of the findings in the 24-month mouse carcinogenicity study regarding the incidences of hepatocellular adenomas and carcinomas in female mice should contain the wording provided in the February 24, 2000 approvable letter. The statement should read,

Response

The description of the findings in the 24-month mouse carcinogenicity study as presented in our June 23, 2000 submission accurately presents the study results and is identical to the description of this study in the approved package insert for PROTONIX® Delayed-Release Tablets (approved February 2, 2000). Therefore, we propose that the statement be retained as,

FDA Comment

7. Revise the **HOW SUPPLIED** section to state the pantoprazole concentration per mL.

Response

The **HOW SUPPLIED** section should only state how the furnished product is supplied. This paragraph has been redacted to contain only this information. In addition, we revised this section to reflect (a) our current container proposal, and (b) the storage requirements for the filters. Also, we modified the manufacturer declaration, "Manufactured for to delete the word

FDA Comment

Additional revisions to the labeling regarding the **DOSAGE AND ADMINISTRATION** section will be conveyed to you following our review of the modified packaging requested.

Response

We propose to modify the **DOSAGE AND ADMINISTRATION** section to reflect the requirement for use of an in-line filter during the administration of PROTONIX® I.V. for Injection and specify the recommended filter type. We understand that additional revisions to this section may be requested following agreement on the container design.

Other – Modification of **ADVERSE REACTIONS** section

We propose to revise the **ADVERSE REACTIONS, Safety Experience of Intravenous Pantoprazole** section in order to focus on adverse reactions that prescribing physicians might be expected to observe with use of PROTONIX® I.V. for Injection, and to avoid the redundancy of listing adverse events already reported in the **Safety Experience of Oral Pantoprazole** section. The proposed modifications also update this section to reflect the safety information provided in the May 2, 2000 safety update to NDA No. 20-988.

We also propose to update the **ADVERSE REACTIONS, Safety Experience of Oral Pantoprazole** section to be consistent with the currently approved package insert for PROTONIX® Delayed-Release Tablets (approved February 2, 2000). This section is identical to currently approved package insert, except for the insertion of the word "oral" to clarify the formulation used to generate the data described.

JAN 12 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: January 14, 2000	DUE DATE: January 28, 2000	OPDRA CONSULT #: 99-105

TO (Division):
Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

PRODUCT NAME: PROTONIX® I.V. (Pantoprazole Sodium for injection) NDA #: 20-988	MANUFACTURER: Wyeth-Ayerst Laboratories

CASE REPORT NUMBER(S): N/A

SUMMARY:
In response to a December 2, 1999, consult from the Division of Gastro-Intestinal and Coagulation Drug Products (HCD-180), OPDRA conducted a review of the proposed proprietary name Protonix® I.V. for Injection to determine the potential for confusion with approved/unapproved proprietary and generic names.

OPDRA RECOMMENDATION:
OPDRA has no objection to the use of proprietary name "Protonix® I.V." In addition, OPDRA concurs with the recommendation from LNC (Label and Nomenclature Committee) on the established name.

/S/ 1/12/2000

Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 827-8173

/S/ 1/12/00

Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

Date of Review: 12/30/99

NDA#: 20-988

Name of Drug: Protonix® I.V.
(Pantoprazole Sodium for Injection)

NDA Holder: Wyeth-Ayerst Laboratories

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products on December 2, 1999, to review the proposed proprietary drug name, Protonix® I.V. in regard to potential name confusion with existing proprietary/generic drug names.

Protonix® I.V. (sterile pantoprazole sodium) was reviewed by the Labeling and Nomenclature Committee (LNC) and found acceptable without the suffix I.V. The Committee recommended removal of the suffix "I.V." from the proprietary name since it may be mistaken for the roman numeral 4 and result in a medication error. LNC further recommended removal of "sterile" from the established name and the addition of "for Injection" since "sterile" is on longer used in the official titles of parenteral products. The firm was informed of LNC's decision, however, the sponsor wishes to retain "I.V." in the name.

Product Information

Protonix® I.V., manufactured by Wyeth-Ayerst Laboratories, was submitted under NDA 20-988 and is indicated for short-term treatment (7-10 days) of gastroesophageal reflux disease (GERD), as an alternative in patients who are unable to continue taking Protonix® Delayed Release Tablets.

Pantoprazole peak serum concentration and area under the serum concentration-time curve increase in a manner proportional to intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinics are unaltered with multiple daily dosing. It is extensively metabolized in the liver through the cytochrome P450 (CYP) system and excreted primarily in the urine.

Protonix® I.V. will be supplied as a freeze-dried powder for reconstitution in a 40 mg/vial strength.

II. RISK ASSESSMENT

In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, Protonix® I.V. with other drug names, the medication error staff of OPDRA searched Microdex online, PDR (1999 Edition), American Drug Index (43rd Edition), Drug Facts and Comparison (updated monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. In addition, OPDRA also searched several FDA databases for potential sound-alike and look-alike names to approved/unapproved drug products through DPR, Medline online, LNC database, EES and DSS. A focus group was conducted to review all the findings from the searches. OPDRA also conducted studies of written and verbal analysis of the proposed proprietary name employing health practitioners within CDER to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

A. STUDY CONDUCTED BY OPDRA

Methodology:

This study involved 90 health professionals consisting of physicians, nurses and pharmacists within CDER to determine the degree of confusion of Protonix® I.V. with other drug names due to the similarity in handwriting and verbal pronunciation of the name. OPDRA staff member wrote two outpatient prescriptions and one inpatient order, each consisting of a known drug product and a prescription for Protonix® I.V. These prescriptions were scanned into the computer and a random sample of the written orders were then delivered to the participating health professionals via e-mail. Outpatient prescriptions and inpatient orders were each sent to 30 participants. In addition, one pharmacist with an accent recorded the outpatient orders on voice mail. The voice mail messages were then sent to the remaining 30 participating health professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

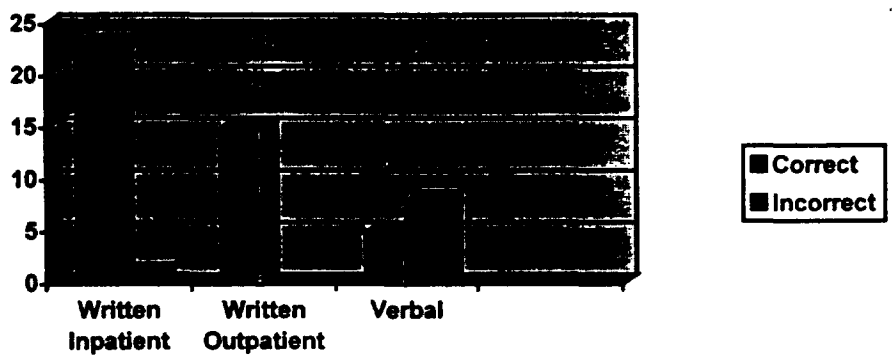
Results:

We received responses from 52 participants (out of 90), forty-three of which interpreted the name correctly. Twenty-four participants interpreted an inpatient order, fifteen interpreted outpatient prescriptions and thirteen interpreted verbal orders.

The results are summarized in Table 1.

Table 1

Study	# of Sample	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	30	24 (80%)	23	1
Written Outpatient	30	15 (50%)	15	0
Verbal	30	13 (43%)	5	8



Eighty-three percent of the participants responded with the correct name "Protonix® I.V.". Ninety-seven percent of the written prescriptions (inpatient/ outpatient) were interpreted correctly, and thirty-nine percent of the verbal orders were interpreted correctly. The incorrect written and verbal responses are as follows:

Written	Verbal
Protinex	Protonet
	Protonex
	Protonex
	Protonex
	Protonex
	Protonex
	Protonex
	Protonec

B. FOCUS GROUP:

The group did not uncover any existing drug names that could cause confusion with Protonix® I.V. and thus pose a significant safety risk. The group did raise concerns with the use of the abbreviation of the dosage form "I.V." in conjunction with the proprietary name. The suffix "I.V." may have the potential to be misinterpreted as the roman numeral 4.

C. DISCUSSION:

The results of the verbal and written analysis studies show forty-three out of fifty-three participants interpreted the proprietary name Protonix® I.V. correctly. There are high scores of correct interpretation of almost all written prescriptions (38 out of 39) for this newly proposed proprietary name Protonix® I.V. Less than half of the verbal prescriptions were interpreted correctly. The incorrect responses pose little concern since Protinex, Protonet and Protonex are not proprietary names that are currently marketed.

Since Focus Group as well as Label and Nomenclature Committee (LNC) raise concerns on proprietary names with suffix "I.V.", a search was conducted to determine if suffix "I.V." can contribute to potential medication errors on those products that are available both in injection and oral dosage forms. There are about nine approved proprietary names that fit this criteria. They are as follows: 1) Vasotec Tablets, Vasotec I.V. Injection, 2) Rifadin Capsules, Rifadin I.V. Injection, 3) Erythrocin Tablets, Erythrocin I.V. Injection, 4) Cipro Tablets, Cipro I.V. Injection, 5) Trovan Tablets, Trovan I.V. Injection, 6) Indocin Capsules, Indocin I.V. Injection, 7) Flagyl Tablets, Flagyl I.V. Injection, 8) Cytovene Capsules, Cytovene I.V. Injection, 9) Sandimmune Capsules, Sandimmune I.V. Injection.

The search through DQRS and AERS (post-marketing) did not reveal any significant safety risk on the above nine products. However, some health professionals did voice concerns on equivalent dosage for Cipro IV and Oral.

For example, Cipro IV 400mg is equivalent to 500mg oral tablets. This may result medication error in calculating the proper equivalent Oral dose from IV. But in the case of Protonix® I.V. , the Oral and IV dose is at 40 mg each. Therefore, the potential risk to misinterpret suffix I.V. as roman numeral 4 and thereby resulting a medication error is unlikely. In fact, from the practicing professionals (physicians, pharmacists and nurses) point of view, the suffix "I.V." can be easily distinguished from the IM dosage. This helps reduce medication error and hence improve safety.

III. RECOMMENDATION

1. OPDRA has no objection to the use of proprietary name "Protonix® I.V.".

2. OPDRA concurs with LNC (Label and Nomenclature Committee) recommendation on the established name.

Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241.

/S/

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur

/S/ 5/12/2000

Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

C.C.

NDA 20-988
Office Files
HFD-180; Maria R. Walsh, Project Manager, DGCDP
HFD-180; Lilia Talarico, Division Director, DGCDP
HFD-440; Ann Corken, Safety Evaluator, DDREII
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1067	HFD#	180	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	MARIA R. WALSH			PROTONIX I.V.	sterile pantoprazole sodium

A. Look-alike/Sound-alike

Potential for confusion:

	Low	Medium	High	
	Low	Medium	High	
	Low	Medium	High	
	Low	Medium	High	
	Low	Medium	High	

B. Misleading Aspects:

The I.V. should be deleted from the brand name since it may be mistaken for the roman numeral 4 and result in a medication error.

C. Other Concerns:

D. Established Name

____ Satisfactory

xxx Unsatisfactory/Reason

Sterile is no longer used in the official titles of parenteral products.

Recommended Established Name

pantoprozole sodium for injection

E. Proprietary Name Recommendations:

XXX ACCEPTABLE WITHOUT THE I.V. ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 4/22/96

CSO/Walsh

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products		**HFD-180**
Attention: Maria R. Walsh, Project Manager	**Phone:** (301) 443-0487	
Date: July 30, 1998		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: Protonix I.V.	**NDA/ANDA#** NDA 20-988	
Established name, including dosage form: sterile pantoprazole sodium		
Other trademarks by the same firm for companion products: Protonix Enteric-Coated Tablets for pending NDA. 20-987		
Indications for Use (may be a summary if proposed statement is lengthy): short-term gastric acid suppression in GERD patients who are unable to take the oral medication (i.e. pantoprazole tablets)		
Initial Comments from the submitter (concerns, observations, etc.): None		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-988; HFD-180/division file; HFD-180/

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6-30-1999

FROM: Lilia Talarico, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products

SUBJECT: Pantoprazole i.v. for short-term gastric acid suppression in GERD patients who are unable to take oral Pantoprazole. Secondary Review

TO: NDA 20-988

THROUGH: Florence Houn, M.D.
Director, Office Drug Evaluation III. CDER

Pantoprazole (Protonix) is a proton pump inhibitor that was deemed approvable for the short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease (GERD) on 6-28-1999. The clinical data of efficacy and safety submitted in NDA 20-988 supported the indication for the use of pantoprazole for up to 8 weeks, with consideration of an additional 8 weeks of therapy in patients who had not initially responded. The recommended dosage of oral pantoprazole was 40 mg po per day.

On July 20, 1998, the sponsor submitted an efficacy supplement for the approval of intravenous (i.v.) pantoprazole for short-term treatment (7 to 10 days) of GERD patients unable to take oral pantoprazole.

In support of the request for approval of the i.v. formulation, the sponsor has submitted data from two clinical trials of pharmacodynamic response (inhibition of gastric acid secretion) as parameter of efficacy.

Two additional open-label studies compared the healing and symptom relief in patients with grade II/III EE treated initially with i.v. pantoprazole followed by oral pantoprazole. Efficacy was assessed by comparison to historical patients treated with oral pantoprazole. These studies were not adequate to support the use of i.v. pantoprazole as initial therapy of EE and GERD nor to be used in support of the requested indication.

Study 3001K1-309-US GMR-32141: "A comparison of gastric secretion responses in patients with gastroesophageal reflux disease who are switched from oral to intravenous pantoprazole."

The study was a pivotal trial designed to demonstrate bioequivalence by comparing basal gastric acid output (BAO) and pentagastrin-stimulated acid output (MAO) response of 20 or 40 mg qd oral pantoprazole administered on day 1 through up to day 14 to 20 or 40 mg qd i.v. pantoprazole infused over 15 minutes on day 11 through 17 in GERD patients with history of erosive esophagitis.

The hypothesis to be tested was that patients who had been stabilized on oral pantoprazole could be effectively and safely switched to i.v. pantoprazole for up to 7-10 days and that i.v. pantoprazole can be used as an alternative formulation in patients who cannot take oral pantoprazole.

The study was randomized, double-blind, multiple-dose, four arm two period, placebo-controlled trial of 65 patients. Patients receiving 20 mg of oral pantoprazole in study period 1 were switched at day 10 to either 20 mg of i.v. pantoprazole or placebo; patients receiving 40 mg oral pantoprazole in study period 1 were switched at day 10 to either 40 mg i.v. pantoprazole or placebo.

The primary efficacy endpoint was the comparison of the mean MAO following the last i.v. pantoprazole dose (MAO_{Liv}) to that following the last oral pantoprazole dose (MAO_{Lpo}) for the 20 and 40 mg treatment groups.
Secondary efficacy endpoints were: 1) comparison between first i.v. dose mean and the last oral dose mean, and 2) comparison between the last i.v. BAO mean to the last oral BAO mean.
Only the results of the 40 mg i.v. dose are addressed in this review because this dose regimen is proposed for replacement of the oral pantopraxole 40 mg/day dose.

Statistical analyses of the data are summarized in the medical review (page 37 and 38) and in the statistical review. The primary analysis was the comparison of the MAO following the last i.v. dose of 40 mg versus the MAO following the last oral dose of 40 mg. The primary efficacy analysis was conducted to test the hypothesis that the MAO of the last i.v. dose would be no more than 20% greater than the MAO of the last oral pantoprazole dose. The results are summarized in the following table:

Primary efficacy endpoint: Comparison of the mean MAO following the last i.v. dose with that following the last oral dose of pantoprazole (MAO_{Liv} - 1.2 MAO_{Lpo})

Study population analyzed:	ITT	M-ITT	VFE
MAO Last day oral (n-30):	4.69 ± 5.62 (0.0-20.3)	6.32 ± 5.87 (0.0-20.3)	6.56 ± 5.84 (Q.0-20.3)
MAO Last Day i.v. (n=23):	6.62 ± 6.34 (0.0-20.3)	6.32 ± 5.87 (0.0-20.3)	6.56 ± 5.84 (0.0-20.3)
Placebo i.v. (n=7)	29.19 ± 13.01 (6.9-48.7)	27.44 ± 15.50 (6.9-48.7)	27.44 ± 15.50 (6.9-48.7)

The p-values for rejecting the null hypothesis of inferiority of MAO_{Liv} to MAO_{Lpo} by 20% of MAO_{Po} or more were all statistically significant at one-side level <0.025. Equivalence on inhibition of AO, both basal and maximal, on the first day of pantoprazole i.v. to the last day of oral pantoprazole was not established.

The claim of non-inferiority for the 20 mg oral pantoprazole versus i.v. was not demonstrated by all statistical analyses. The results of the secondary efficacy endpoint analyses were also variable.

By every statistical analyses, the last MAO following i.v. pantoprazole was significantly lower than that obtained with i.v. placebo.

Intravenous pantoprazole was safe and well tolerated throughout the study period.

STUDY 3001K1-100-US: "A dose-range study of inhibition of pentagastrin induced gastric-acid secretion by single doses of intravenous pantoprazole, intravenous famotidine and oral pantoprazole."

This study was an open-label trial conducted in healthy volunteers. The objectives of the study were: 1) to assess the magnitude and time course of inhibition of pentagastrin-stimulated gastric acid secretion by various doses of i.v. pantoprazole as a model for patients with ZE syndrome, and, 2) to compare these variables with those induced by oral pantoprazole, intravenous famotidine and placebo, and, 3) to determine the pharmacodynamic dose response of pantoprazole i.v. over a dose range of 20, 40, 60, and 120 mg.

The PD response was evaluated using reduction of gastric acid output (AO) to less then 10 mEq/h as the cut-off point. Using this pharmacodynamic model, the pantoprazole i.v. doses of 20, 40, 80 and 120 mg were compared to each other, to oral pantoprazole 40 mg, to famotidine i.v. and to placebo i.v..

The study was conducted in normal volunteers, however, the results can be extrapolated to GERD patients since it has been demonstrated that esophagitis and its complications, are not related to high acid output and pepsin secretion.

Whereas the results of the higher doses of pantoprazole i.v. were assessed for their potential therapeutic indication for Z-E syndrome, the comparison between i.v. and oral pantoprazole 40 mg/day is used to support the bioeqiovalence of the two regimens.

The results showed that pantoprazole 40 mg i.v. reduced cumulative acid output (AO) compared to placebo and was as effective as the 40 mg oral dose.
Intravenous pantoprazole was found to be safe in the study population and for the study duration.

On the basis of the PD results from the above two studies, the sponsor has requested approval to market the 40 mg pantoprazole intravenous formulation for the indications limited to short-term use only in GERD patients unable to take the oral pantoprazole formulation.

Concerns for potential carcinogenicity and genotoxicity were raised for the oral pantoprazole formulation and additional studies are planned by the sponsor as Phase IV commitments . There is no indication that the intravenous formulation may have a different safety profile, however, the benefits of the i.v. formulation appear to be clinically more relevant because there is no proton pump inhibitor that is available for parenteral use and pantoprazole would fulfill a medical need. Therefore, approval of the i.v. formulation of pantoprazole at the dose of 40 mg/day for the above indication is recommended.

The indication requested by the sponsor are restrictive since the i.v. pantoprazole could only substitute oral pantoprazole rather than any other oral proton pump inhibitor.
In order to bridge the i.v. pantoprazole to other proton pump inhibitors, the sponsor should consider conducting the appropriate clinical trial to assess the efficacy of the i.v. pantoprazole for treatment of erosive esophagitis and GERD or by showing PD equivalence of i.v. pantoprazole and other proton pump inhibitors on inhibition of gastric acid secretion.

/S/
Lilia Talarico, M.D.

cc:
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-torres
HFD-181/MWalsh
HFD-180/JChoudary
HFD-180/EDuffy
HFD-103/FHoun
HFD-103/VRaczkowski
f/t 7/7/99 jgw
N/20988907.0LT

NDA No. 20-988

PATENT INFORMATION UNDER SECTION 505(b)

PROTONIX™ I.V. (sterile pantoprazole sodium, injectable) is covered by U.S. Patent 4,758,579 which claims the drug substance. The normal expiration date of said patent is July 19, 2005. An application for extension of said date under the terms of the Drug Price Competition and Patent Term Restoration Act of 1984 will be filed upon approval of the NDA. Patent Information will be updated upon issuance of a certificate of patent term extension. The applicant is the exclusive licensee of this patent. In the opinion of applicant and to the best of applicant's knowledge, there is no other U.S. patent which claims the drug for which applicant has sought approval or which claims the use of the drug for which applicant has sought approval.

WYETH-AYERST LABORATORIES

By: _____
Arthur G. Seifert
Patent Attorney

Patent/Exclusivity Information

1)	Active Ingredient(s)	Sterile Pantoprazole Sodium
2)	Strength(s)	40 mg.
3)	Trade Name	PROTONIX™ I.V.
4)	Dosage Form (Route of Administration)	Vial, Injectable
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	20-988
7)	Approval Date	TBD
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(iii) and 505(c)(3)(D)(iii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this application. [Based on concurrent or prior approval of NDA 20-987 (PROTONIX™ Tablet)]
9)	Applicable patent numbers and expiration date of each	U.S. Patent 4,758,579, Normal Expiration Date: July 19, 2005.

PROTONIX™ (sterile pantoprazole sodium) I.V.

NDA No. 20-988

Item 16. Certification Required by Generic Drug Enforcement Act of 1992

The undersigned certifies that Wyeth-Ayerst did not and will not knowingly use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)] of the Generic Drug Enforcement Act of 1992 in connection with NDA No. 20-988 PROTONIX™ (sterile pantoprazole sodium) I.V.

Signed: _____

Justin R. Victoria
Vice President, Worldwide Regulatory Affairs