CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-020

SUMMARY REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 11/14/07

FROM: Joyce A Korvick, MD, MPH

DGP/ODE III

SUBJECT: Deputy Division Director Approval Review
NDA 22-020

APPLICANT: Wyeth Pharmaceuticals

DRUG: PROTONIX ® (pantoprazole sodium) For Delayed-Release Oral Suspension (40 mg)

DIVISION RECOMMENDATION:
The clinical pharmacology and medical review teams recommend approval based upon the review of the responses received August 1, 2007 in response to our approvable letter, March 15, 2007. I concur.

Regulatory History:
In the March 15, 2007 letter the following deficiencies were listed:

> "An FDA Division of Scientific Investigations (DSI) audit of the [ ] facility conducting the pharmacodynamic (PD) comparability study titled "A Randomized, 2-Period, Crossover, Pharmacodynamic Comparability Study Comparing a Pantoprozole Sodium Spheriod Formulation to the Currently Marketed Tablet Formulation in Subjects with GERD and a History of Erosive Esophagitis" (3001-B1-332-US) has found that the analytical data for the PD endpoint in this study are not acceptable for review, because of insufficient method validation, calibration, quality control, and documentation. Therefore, data from this PD study cannot be used to support this NDA. Without valid PD comparability data, or data demonstrating bioequivalence to the reference listed product, the safety and efficacy of Protonix Delayed Release [ ] cannot be determined. If these deficiencies cannot be resolved, you will need to perform an additional PD study to support an approval of your application." b(4)

Wyeth chose to respond to the deficiencies and the report from DSI in the current complete response submission. The clinical pharmacology review team found the response adequately addressed the issues raised by DSI to their satisfaction. Therefore, they recommended approval with specific comments to the label. The clinical review

team also agreed with approval based upon the findings in the clinical pharmacodynamic study mentioned above. Please refer to clinical pharmacology and medical officer review for additional details. In my previous Addendum (Division Director AE Memo) I outline the basis for the acceptability of the approach to utilize the pharmacodynamic study as the basis of approval. Please refer to that memo for additional details. Given that the sponsor was able to satisfactorily respond to the issues raised by the DSI review and clinical pharmacology reviewers, I find it acceptable to approve this formulation for the currently approved "Tablet" indications: Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD), Maintenance of Healing of Erosive Esophagitis, and Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome.

PREA Responses:
(These responses were discussed with the Pediatrics Division and were acceptable.)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

Waived Studies: the pediatric study requirement for ages birth to seventeen years for the treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome.

Deferred Studies: studies for ages birth to seventeen years for short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease and for maintenance of healing of erosive esophagitis in this application.

The deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study under PREA for the treatment of erosive esophagitis associated with gastroesophageal reflux disease in pediatric patients ages birth to seventeen years.
Final Report Submission: December 31, 2008

2. Deferred pediatric study under PREA for the maintenance of healing of erosive esophagitis in pediatric patients ages birth to seventeen years.
Final Report Submission: December 31, 2008

Labeing:
Please see final attached to the Approval Action Letter, November 14, 2007.

One final issue was addressed in this label regarding drug-drug interactions. In order to be consistent with the information in the Atazanavir label regarding drug interactions, the following "class labeling" was added to the Precautions section of the label:

"Concomitant use of atazanavir and proton pump inhibitors is not recommended. Coadministration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect."

[redacted] The Atazanavir [redacted] b(4)

labeling was based upon studies performed utilizing omeprazole.

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/s/

Joyce Korvick
11/14/2007 11:57:47 AM
MEDICAL OFFICER

ATTENTION ADDENDUM (3/15/07)

ADDENDUM 3/1/07: New Regulatory Action: I recommend an approvable action be taken on this NDA.

At 3:30 PM, 3/15/07 Wyeth Pharmaceuticals submitted an amendment to the NDA which attempted to address the [ ] deficiencies. In this document Wyeth expresses the opinion that issues can be adequately addressed and satisfactorily resolved so that these data from the pivotal study would be able to be relied upon for an approval action. Based upon the arguments in this new submission, the encouraging study results, and given the timing of the official DSI communication to [ ] and in consultation with the Clinical Pharmacology reviewer I now recommend an approvable action. b(4)

Please not that remarks made below are from my original signed review. While the data remain the same the action recommendation has changed since its writing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

MEMORANDUM

DATE: 3/14/07

FROM: Joyce A Korvick, MD, MPH

DGP/ODE III

SUBJECT: Deputy Division Director Action Recommendations

APPLICANT: Wyeth Pharmaceuticals

DRUG: NDA 22-020
Protonix® (pantoprazole sodium)
Delayed-Release [ ] Oral Suspension, 40 mg. b(4)

DIVISION RECOMMENDATION:

I recommend that this supplemental application be "Not Approved".

This recommendation is based upon the results of a DSI (Division of Scientific Investigation) Site Inspection. There were significant deficiencies found at the analytical site for the pivotal trial, [ ]. In a memo from the field dated b(4)

ATTENTION ADDENDUM (3/15/07)

12/22/06, the division was notified of these deficiencies and the recommendation by DSI regarding the lack of usefulness of this pharmacodynamic study. This occurred in the pivotal study for the formulation change.

In addition, bioequivalence was not demonstrated between the proto-type granule formulations and the to-be-marketed granule product.

I. Regulatory History:

Protonix delayed-release tablet (NDA 20-987) was approved in the United States in February 2000 for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis (EE). Subsequently, NDA 20-987/S-001 was approved on June 12, 2001 for the maintenance of healing of EE and control of daytime and nighttime heartburn symptoms in subjects with GERD. NDA 20-987/S007 was approved for pathological hypersecretory conditions including Zollinger-Ellison Syndrome (ZES) on April 19, 2002.

The sponsor originally developed the granule formulation in response to a Pediatric Written Request (WR) from the FDA (December 2001), which required an age-appropriate formulation for the study of pantoprazole sodium in clinical trials in infants and children. The sponsor subsequently developed the granule formulation (equivalent to 40 mg pantoprazole) as an alternative to the marketed tablet formulation intended for patients with GERD and a history of EE who are unable to swallow the tablet. At the recommendation of the FDA, the dosage name was changed from "spheroids" to "granules".

On April 30, 2004 the sponsor requested a Type C meeting with the FDA, and sent a meeting background package detailing a pharmacodynamic (PD) equivalence approach to bridge the commercial pantoprazole sodium delayed-release granules to the marketed pantoprazole sodium delayed-release tablet. The PD equivalence approach proposed a two-period crossover study in patients with GERD and a history of EE, with pentagastrin stimulated maximum acid output (PG-MAO) as the primary parameter and 24-hour pH (AUC) as the secondary PD parameter. This approach while not optimal, was acceptable (refer to meeting minutes).

On May 12, 2006 the new drug application (NDA) for Protonix® (pantoprazole sodium) Delayed-Release[redacted]40 mg. was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. It included 5 clinical pharmacology studies in support of this formulation change. b(4)

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

The proprietary name was found acceptable by DDMAC. Since we are recommending a "Not Approvable" action, there are no labeling comments to consider at this time.

B. Chemistry and Manufacturing:

ATTENTION ADDENDUM (3/15/07)

The review found this product acceptable. The chemistry review team suggests that the appropriate name is Protonix (pantoprazole sodium) for Delayed-Release Oral Suspension, 40 mg, in order to be consistent with previous approvals.

C. Pre-Clinical Pharmacology/Toxicology:
Not Applicable, no additional pre-clinical data were submitted.

D. Clinical Pharmacology:
The following studies were considered central to the review of this application:

Study Number: 3001B1-332-US
Study Description: A randomized, 2-period, crossover, pharmacodynamic comparability study comparing a pantoprazole sodium delayed-release granules formulation to the currently marketed tablet formulation in subjects with GERD and a history of erosive esophagitis (EE).
Number of Subjects: 76

Study Number: 3001B1-116-US
Study Description: An open-label, randomized, 3-period, crossover, bioequivalence study of the to-be-marketed formulation of pantoprazole sodium delayed release granules administered in 3 dose regimens to healthy subjects.
Number of Subjects: 25

Study 3001B1-332-US, a pharmacodynamic study, was considered pivotal. Relying on a pharmacodynamic study was considered appropriate because of the type of formulation change: tablets to granules. Each packet was filled with enteric coated granules containing 45.1 mg of pantoprazole sesquihydrate (equivalent to 40 mg of pantoprazole). It was anticipated that strict bioequivalence would not be demonstrated between the tablet and delayed release granules for oral suspension. In addition, Wyeth performed several other studies to address the issues of administration in various vehicles (apple juice, apple sauce) and via different routes: nasogastric tube. These later studies were performed with proto-type granules and not the to-be-marketed product. Study 3001B1-116-US was central for the testing of the delivery vehicle (apple sauce, apple juice and NG tube), given the importance of maintaining stability of the enteric coating.

The results of Study 3001B1-332-US are displayed below:

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Table 2. Summary Statistics for Maximum Acid Output (mEq/h) by Formulation, Modified Intent-to-Treat (MITT) Population		
Statistics	**Granule 40 mg**	**Tablet 40 mg**
N	52	52
Mean ± SD	7.11 ± 4.98	7.29 ± 4.77
Median	6.69	6.85
Min, Max	0.56, 23.62	0.58, 18.96

Abbreviations: SD=standard deviation; Min=minimum; Max=maximum. Source: Table9.4.1.1.-2

The clinical pharmacology reviewer notes that the results were similar, however, the statistical test, using a one-sided approach was not valid. When a two-sided test is applied the null-hypothesis is rejected. The clinical interpretation of these results is discussed in the clinical section. There two outliers in the granule results, this may be due to the delivery of the granules, or the potential effect of the ⊏ ⊐ methods. This may effect the overall calculation of the MAO. It should be noted that a lower mean MAO would be interpreted as being more acid suppressing and potentially more effective. This endpoint can be used in conjunction with other pharmacodynamic endpoints to bridge these types of formulations; however, if the differences were clinically significant the applicant would have to perform an efficacy study. From my point of view, we will defer the interpretation of this study until the sponsor addresses the DSI comments, or performs a new study.

b(4)

The clinical pharmacology reviewer had the following comments regarding the second study:

Study # 3001B1-116-US was carried out to establish bioequivalence among the 3 proposed methods for administration (sprinkled on applesauce, mixed with apple juice, and administered through a nasogastric [NG] tube with apple juice) of the granules. This was an open-label, single-dose, randomized, 3-period crossover study in healthy adult subjects. Administration of the granules with applesauce was found to be bioequivalent to administration with apple juice but it was not bioequivalent to administration via a nasogastric tube in apple juice

- *For Cmax, AUCT, and AUCinf, the 90% CI's for the ratio of the geometric means of the granules in apple juice to granules sprinkled on applesauce were within the BE limits of 80-125%.*
- *The 90% CI's for the ratio of the geometric means for Cmax, AUCT, and AUCinf, of the granules delivered via nasogastric (NG) tube in apple juice to granules in applesauce were not within the BE limits of 80-125% when all subjects were included.*
- *However, the exclusion of the three subjects who only received a small fraction of the dose due to trapping of the majority of the dose in the clogged NG tube resulted in the 90% CI's for the ratio of the geometric means for Cmax, AUCT, and AUC, of the granules delivered via nasogastric (NG) tube in apple juice to granules in applesauce being within the BE limits of 80-125 %.*

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These issues can be dealt with in labeling, however, the clinical pharmacology reviewer when on to state that the test article in these studies is not the to-be-marketed product and there is no bridge to that product. This deficiency will have to be addressed in the response to the NA action.

E. Clinical/Statistical:

The medical reviewer had the following comments regarding the pharmacodynamic results described above:

Efficacy:
Efficacy studies were not submitted with this NDA. Instead, data submitted by the sponsor demonstrate the pharmacodynamic comparability between pantoprazole granules and pantoprazole tablets. To this end, study 3001B1-332-US showed that pantoprazole granules were comparable to the delayed-release tablets formulation in suppressing pentagastrin stimulated maximum acid output (PG-MAO) in patients with GERD and a history of EE. The overall mean PG-MAO and standard deviation for all subjects was 7.11 ± 4.98 mEq/h and 7.29 ± 4.77 mEq/h for the granule and the tablet formulation, respectively.

The primary pharmacodynamic endpoint, MAO, is identical to that used in study 3001K1-309-US, which was the basis for the approval of the intravenous formulation of pantoprazole (NDA20-988). This is an established and proven endpoint, and was used in NDA20-988 to demonstrate the same [equipotent/equivalent] antisecretory effects between two different formulations (intravenous and oral) where PK data (i.e., Cmax) cannot be obtained.

The medical officer conclusions are as follows:

- The MAO for the 2 formulations were comparable for the 3 analysis populations (mITT, VFE, and ITT).
- There were no clinically meaningful differences in BAO between the 2 formulations for the 3 analysis populations (mean and median BAO less than 1 mEq/h).
- The 24-hour pH-metry also demonstrated similar results with the 2 formulations
- Median intraesophageal pH, median intragastric pH, and percentage of time that intraesophageal pH was <4 demonstrated no statistically significant differences between the 2 formulations in the mITT population
- The other secondary pH variables with greater variability demonstrated similar results between the 2 formulations

Although the sponsor submitted PD comparability data between the granule and tablet formulation, due to irregularities uncovered during a DSI audit, the integrity of that data cannot be established.

Safety: No new safety signals.

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F. Pediatric Use:
Deferred EE and Waived ZE.

III. DSI Findings:
DSI recommends that the analytical data for the pharmacodynamic endpoint in study 3001B1- 332-US are not acceptable for review, because of insufficient method validation, calibration, quality control, and documentation. (Field Report: 12/22/06)

The following findings were shared with the site upon inspection and DSI sent an EIR to ⊏ ⊐ on 3/5/07 which contains similar details regarding the analytic procedures: b(4)

⊏ ⊐
Study 3001B1-332-US b(4)

1. Failure to demonstrate the performance of the assay for titratable acid in gastric Aspirates

A. Individual runs were not conducted with calibrators and quality control samples at multiple concentrations. Runs were accepted on the basis of a single "titration check" sample, consisting of 0.1 N HCl in water.

B. There was no demonstration that the assay was not affected by shipment of sample tubes with dry ice, or the presence of particulates, salts, and other normal constituents of gastric fluids. Some samples were shipped frozen from the clinical sites in dry ice, in violation of the protocol. Samples were not centrifuged or filtered to remove particulates.

C. There was no evaluation of recovery of HCl added to samples of gastric aspirates.

D. There was no measurement of, or adjustment for, titratable acid in reagent blanks.

E. The assay did not confirm increased acid secretion in a "maximal acid output" validation sample relative to its "basal acid output" validation sample. The single samples were used for evaluating storage stability. The stimulation for the maximal acid output sample was said to be "cephalic-vagal" stimulation, without a further definition available from the outside collection site. Although it was recognized at the time that the stimulation failed to increase acid output, and possibly caused samples to be diluted with saliva, the stability experiment was not repeated.

2. Failure to retain records of laboratory operations performed for validation and testing. Only observations, intermediate calculations, and reported results were retained.

3. Two runs were accepted although the "titration check" results were outside the specified acceptance limits ⊏ ⊐ of true concentration). Examples: two runs on 7/15/2005 b(4)

4. The analyst did not sign and date all original data entries on the day of acquisition.

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5. Only the first page of autotitrator displays was printed. The second page, with data for titration to the pH 7.0 endpoint, was not printed. The acid output calculations relied solely on titrations to pH 7.0.

IV. Labeling Recommendations:

No labeling recommendations will be made at this time due to the significant deficiencies in the application and recommended not approvable action.

V. Phase IV Commitments:

Not applicable

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/s/

Joyce Korvick
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