

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-020

MEDICAL REVIEW(S)

MEMORANDUM TO THE FILE
DIVISION OF GASTROENTEROLOGY PRODUCTS
Addendum to Medical Officer's Review

NDA: 22,020

Drug: Protonix® for Delayed-Release Oral Suspension

Date: November 11, 2007

Reviewer: Dr. Nancy Snow, Medical Reviewer
HFD-180

Team Leader: Dr. Hugo Gallo-Torres
HFD-180

BACKGROUND:

The NDA for Protonix for delayed-release oral suspension was originally submitted May 12, 2006. The submission was given an "approvable" status by the Division of Gastroenterology Products on March 15, 2007 due to "flaws in the method validation, calibration, quality control, and documentation" of the analytical data as identified during a DSI inspection.

The sponsor has provided a "complete response" to the approvable action with an amendment to the NDA, and additional information on Study 3001B1-116-US, as requested by the FDA. Among the items submitted by the sponsor are:

- Supporting evidence that the assay method and operating procedures used for the pharmacodynamic (PD) endpoint in study 3001B1-332-US met the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendment (CLIA) standards required for clinical diagnostic laboratories.
- List of all samples that were excluded (due to use of dry ice and mishandled samples) from statistical analysis in study 3001-B1-332-US, the pharmacodynamic comparability study. The list contained all the samples excluded in the original NDA plus the three additional subjects (000056, 000060 and 000114) who were identified in the FDA, DSI establishment report (EIR).
- Complete report and data set for the additional analysis for the primary endpoint, maximum acid output (MAO). In the additional analysis, data from the three subjects identified by the FDA EIR report were excluded. The analysis indicated that the results of the additional analysis are similar to those obtained with the original analysis for study 3001-B1-332-US. This finding supports the conclusion

that the proposed delayed-release granules for oral suspension and the delayed-release enteric-coated tablet formulation are comparable in suppressing pentagastrin-stimulated MAO in patients with GERD and a history of EE.

LABELING CHANGES:

The interdisciplinary review team has reviewed the sponsor's proposed labeling, and proposed some slight modifications. The proposed labeling, with modifications, was sent to the sponsor on November 6, 2007. The sponsor's response was received November 7, 2006.

The following sections of the label have particular relevance to clinical practice. Other sections, relating to clinical pharmacology, are addressed in a separate review by the Clinical Pharmacologist.

PRECAUTIONS/DRUG INTERACTIONS

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ADVERSE REACTIONS

The adverse reaction profile for PROTONIX® (pantoprazole sodium) for Delayed-Release Oral Suspension is similar to the established safety profile of PROTONIX® (pantoprazole sodium) Delayed-Release Tablets.

Medical Officer's Comment:

The addition of this sentence is acceptable based on the establishment of PD comparability between the granules for oral suspension and delayed release tablets.

DOSAGE AND ADMINISTRATION

- PROTONIX for Delayed-Release Oral Suspension should be administered in applesauce or apple juice approximately 30 minutes prior to a meal. See Administration Options subsection below. Patients should be cautioned that PROTONIX Delayed-Release Tablets and PROTONIX for Delayed-Release Oral Suspension should not be split, chewed or crushed.
- PROTONIX for Delayed-Release Oral Suspension should only be administered in apple juice or applesauce, not in water or other liquids, or foods.

Medical Officer's Comments:

The above information reiterates that the studies were not conducted mixing the product in water. The studies were done with apple juice or applesauce only. Hence the PD comparability is based on administration in apple juice or applesauce only.

ADMINISTRATION OPTIONS

PROTONIX For Delayed-Release Oral Suspension - Oral Administration in Applesauce:

- Open packet.
- Sprinkle intact granules on one teaspoonful of applesauce.
- Swallow within 10 minutes of preparation.

PROTONIX For Delayed-Release Oral Suspension - Oral Administration in Apple Juice:

- Open packet.
- Empty intact granules into a small cup containing 5 mL of apple juice (approximately one teaspoonful).
- Stir for 5 seconds and swallow immediately.
- To ensure complete delivery of the dose, rinse the container once or twice with apple juice to remove any remaining granules and swallow immediately.

PROTONIX For Delayed-Release Oral Suspension – Nasogastric Tube Administration

For patients who have a nasogastric tube in place, PROTONIX For Delayed-Release Oral Suspension can be administered as follows:

- Separate the plunger from the barrel of a 2 ounce (60 mL) catheter tip syringe.
- Connect the catheter tip of the syringe to a 16 French (or larger) nasogastric tube.
- Hold the syringe attached to the tubing as high as possible during application steps to prevent any bending of the tubing in order to provide smooth flow of contents under gravity.
- Empty the contents of the packet into the barrel of the syringe.
- Add 10 mL of apple juice and gently tap and/or shake the barrel of the syringe to help empty the syringe.
- Add an additional 10 mL of apple juice and gently tap and/or shake the barrel of the syringe to help rinse the syringe and the nasogastric tube. Repeat with at least 2 additional 10 mL aliquots of apple juice. No granules should remain in the syringe.
- Make sure the nasogastric tube is not clogged to ensure that patients receive the full dose.

Medical Officer's Comments:

This information provides detailed instructions on the use of this product in patients with nasogastric tubes. The aim is to try to ensure that patients receive the full dose, by checking the syringe and nasogastric tube to make sure no granules remain, and that blockage of the tube is not an obstacle to administration of the granules.

As noted in the Clinical Pharmacology Review:

“In study 3001B1-116-US, the applicant reported that three subjects (#s 0005, 0016 and 1005) were excluded from the bioequivalence (BE) testing because these subjects did not

receive the protocol specified dose via the NG tube, as majority of the dose was trapped in the clogged NG tube. Although exclusion of the 3 subjects resulted in bioequivalence, there is still the concern that administration through the NG tube may not be interchangeable with sprinkling on applesauce due to problems with clogging of the NG tube. In addition, administration of the granules delivered via the nasogastric (NG) tube was not bioequivalent to administration of the granules in applesauce when the 3 subjects were included in the analysis. There is the concern that administration through the NG tube may not be interchangeable with sprinkling on applesauce due to problems with clogging of the NG tube if, adequate precautions are not taken to prevent the clogging of the tube.”

This MO believes the above wording in the label alerts practitioners that in order for patients to receive a full dose of the product, no granules remain in the syringe or nasogastric tube.

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/s/

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11/7/2007 01:38:17 PM
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**Division of Gastroenterology Products
Clinical Review**

Application Type NDA 22,020
Submission Date 5/12/06

PDUFA Goal Date 3/15/07

Drug Protonix® Delayed-Release
□ □
Therapeutic Class Proton Pump Inhibitor

Applicant Wyeth Pharmaceuticals, Inc.
Regulatory Contact Jethro Ekuta, D.V.M., Ph.D.
Director II
Global Regulatory Affairs
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Priority Designation S

Formulation Delayed-Release Granules
Dosing Regimen 40 mg daily

Indication Short-term treatment of patients with
GERD and a history of EE, Maintenance of
healing of EE, and long-term treatment of
pathological hypersecretory conditions

Intended Population Adults ≥ 18 years old

Reviewer Dr. Nancy F. Snow
Medical Officer
HFD-180

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approval of this application for Protonix® (pantoprazole sodium) delayed release ☐ ☐ is not recommended. The sponsor has submitted results of two pivotal studies to support this efficacy supplement; study 3001B1-332-US, which demonstrated pharmacodynamic comparability between Protonix granules and Protonix tablets, and study 3001B1-116-US which demonstrated bioequivalence between granules mixed with applesauce, apple juice, and apple juice given through a nasogastric (NG) tube. In addition, results of three studies {3001A1-114-US, 3001A1-115-US, 3001A1-118-US} were submitted that contain information about bioavailability and safety of a pilot granules formulation in healthy volunteers. Although comparability has been demonstrated, the sponsor has not submitted data demonstrating the bioequivalence of the to-be-marketed granules formulation to the currently approved and marketed tablet formulation.

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In addition, an audit by the FDA Division of Scientific Investigations (DSI) of the facility conducting PD comparability study 3001-B1-332-US has found that the analytical data for the pharmacodynamic endpoint in this study are "not acceptable for review, because of insufficient method validation, calibration, quality control, and documentation." Therefore data from study 3001-B1-332 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 granules cannot be determined.

1.2 Recommendation on Postmarketing Actions

N/A

1.3 Risk Management Activity

N/A

1.3.1 Required Phase 4 Commitments

N/A

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1.4 Summary of Clinical Findings

1.4.1 Brief Overview of Clinical Program

Pantoprazole sodium is a proton pump inhibitor that is currently approved in a tablet form for the following indications; short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis (EE), maintenance of healing of EE and control of daytime and nighttime heartburn symptoms in subjects with GERD, and the long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome.

The current application (NDA 22-020) is being submitted to support the use of delayed-release granules as a new dosage form of pantoprazole. The enteric-coated granules formulation has been developed to allow for the oral administration of pantoprazole to adult patients when they are unable to swallow tablets. Included in this group are patients with esophageal structural anomalies, esophageal dysmotility and dysphasia, geriatric patients, or those who receive nutrition and medication through feeding tubes. The proposed granule formulation may be administered by three methods: a) oral administration in applesauce; b) oral administration in apple juice; c) administration through a nasogastric tube.

Five clinical studies have been performed to support this NDA. Three (3001A1-114-US, 3001A1-115-US, and 3001A1-118-US) were pilot studies conducted to examine pharmacokinetic characteristics of pantoprazole granules under various conditions, and assisted the sponsor with product development. The delayed-release granules used in the three pilot studies were a developmental prototype.

The two other two studies (3001B1-332-US and 3001B1-116-US) were pivotal trials conducted to support the use of granules as an alternative to the marketed pantoprazole tablet formulation.

Study 3001B1-332-US:

Study 3001B1-332-US was a Phase 3, 2-period, 2-sequence crossover study in subjects with GERD and a history of EE. The study compared pantoprazole delayed-release granules with the currently marketed pantoprazole tablet. The primary purpose of the study was to demonstrate pharmacodynamic comparability of the granules to the tablet, by measuring pentagastrin stimulated maximum acid output (MAO) after administration of 6.0 µg/kg of pentagastrin and 40-mg of either the granules or tablet formulation daily for 1 week. Safety data were also collected.

Secondary objectives included a description of steady-state profiles of several additional pharmacodynamic endpoints: basal acid output (BAO); integrated gastric acidity; mean and median intragastric pH; mean and median intraesophageal pH; percentage of time that intragastric pH was >3 and percentage of time that intragastric pH was >4; percentage of time that intraesophageal pH was <4; number of reflux episodes; number of reflux episodes longer than 5 minutes; and duration of the longest reflux episode.

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Medical Officer's Comment:

In Study 3001B1-332 pentagastrin, administered at maximally stimulatory doses, was used as a diagnostic tool to stimulate the secretion of gastric acid and thus measure the ability of a pantoprazole tablets and granules to suppress gastric acid output. The sponsor intended to use the results of this study to demonstrate pharmacodynamic comparability between the granule and tablet formulation.

Study 3001B1-116-US:

Study 3001B1-116-US was a Phase 1, open-label, single-dose, randomized, 3-period, 6-sequence crossover, inpatient study of healthy adult subjects. Doses of pantoprazole were administered after an overnight fast of at least 10 hours. Each subject received a single 40 mg dose of pantoprazole in each of 3 regimens (single 40 mg dose of pantoprazole granules sprinkled over applesauce, single 40 mg dose of Protonix delayed-release granules mixed with apple juice, and single 40 mg dose Protonix delayed-release granules mixed with apple juice and given through an NG tube). The purpose of the study was to demonstrate bioequivalence of the granules mixed in apple juice, and granules mixed in apple juice and given through a nasogastric tube, to granules mixed in applesauce. However, bioequivalence has not been established between the granules formulation and the tablet formulation.

Medical Officer's Comment:

The sponsor has identified study 3001B1-332-US, as the pivotal study in support of this application for a new dosage form of pantoprazole. Therefore, study 3001B1-332-US is the primary focus of this review, with reference to study 3001B1-116-US, or other studies, as warranted.

1.4.2 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 granules formulation and the tablets formulation, respectively.

Study 3001-116-US demonstrated that the mean C_{max} , AUC_T , and AUC for the granules administered in apple juice and through a nasogastric (NG) tube are similar to those administered in apple sauce. For the C_{max} , AUC_T , and AUC, the 90% CI (Confidence Interval) for the ratio of the geometric means of the granules in apple juice and the granules administered through an NG tube were within the bioequivalence (BE) limits of 80% to 125%. Therefore, granules administered with apple juice and through an NG tube are bioequivalent to granules administered with applesauce.

Medical Officer's Comments:

The studies were designed to demonstrate that Protonix granules are comparable to Protonix tablets in their ability to suppress acid output when stimulated by pentagastrin, and this objective was met. Further, three alternative vehicles for oral administration of the granules were found to be bioequivalent, thus providing three options for the administration of the granules. While pantoprazole granules administered in applesauce, apple juice, and through an NG tube are bioequivalent to each other, this is not a finding of bioequivalence of any of the granule forms to the approved protonix tablet formulation.

1.4.3 Safety

Both formulations of pantoprazole were well tolerated. There were no findings that raised new safety concerns or trends of clinical importance. Adverse events identified with both formulations were consistent with the known safety profile of the drug.

Medical Officer's Comments:

The safety data submitted for the Phase 1 bioequivalence study, and the Phase 3 pharmacodynamic comparability study did not raise new safety concerns.

1.4.4 Dosing Regimen and Administration

The draft label for the current submission provides the following administration options for a once daily 40 mg unit dose of Protonix granules:

- Oral administration in Applesauce
- Oral administration in Apple juice
- Administration through a Nasogastric Tube

1.4.5 Drug-Drug Interactions

No new drug-drug interactions were noted.

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2 INTRODUCTION AND BACKGROUND

Pantoprazole sodium (Protonix®), is a proton pump inhibitor (PPI) that inhibits the final pathway of secretion, the H⁺/K⁺-ATPase (the "proton pump") of gastric parietal cells. It belongs to a group of substituted benzimidazoles, and it produces a rapid and long-lasting reduction of gastric acid secretion, independent of the mode of stimulus of this secretion. A weak base, it is activated by protonation in the strongly acidic conditions inside the parietal cell canaliculus. The protonated form is converted into the active principal, a cyclic sulfenamide. Protonation of pantoprazole also prevents its transport back out of the parietal cell canaliculus. The activated form binds covalently to the available cysteines of H⁺/K⁺-ATPase, forming a tetracyclic sulfenamide. This causes inhibition of gastric acid secretion until more enzyme is synthesized, thus accounting for the prolonged (greater than 24 hours) antisecretory effect.

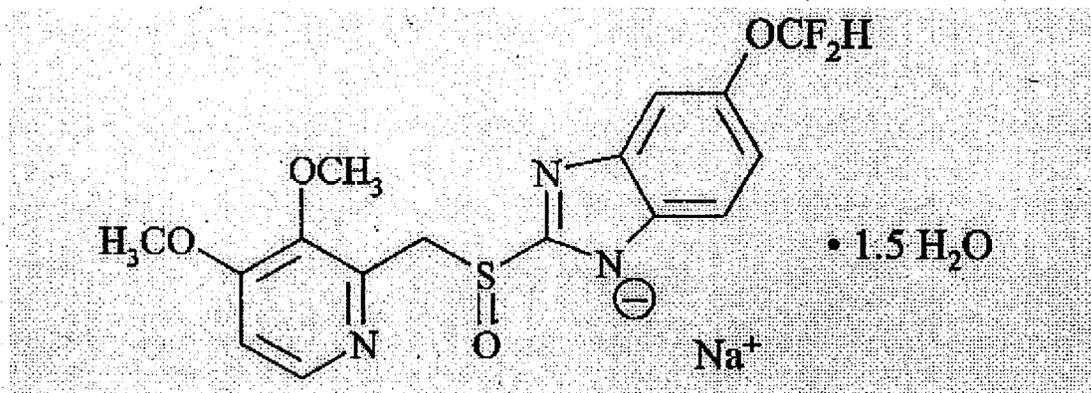
Pantoprazole was developed in the United States by Wyeth Research for oral and I.V. use for conditions in which a reduction in gastric acid secretion is clinically indicated. Pantoprazole 40-mg tablets (NDA20-987) were approved on Feb. 2, 2000 for short-term treatment in the healing and symptomatic relief of EE associated with GERD. Protonix tablets are indicated for the short-term treatment of EE associated with GERD, maintenance of healing of EE, and pathological hypersecretory conditions such as ZES.

Through this submission the sponsor is seeking to gain approval for pantoprazole enteric-coated granules, in order to allow for the oral administration of pantoprazole to adult patients as an alternative when they are unable to swallow tablets. The granule formulation may be orally administered to adults by 3 methods: a) oral administration in applesauce; b) oral administration in apple juice; c) through nasogastric (NG) tube administration.

2.1 Product Information

Trade Name (established name): Protonix® Delayed-Release (Pantoprazole Sodium)

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Proposed Indication: Short-term treatment of patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE), maintenance of healing of EE, and long-term treatment of pathological hypersecretory conditions. b(4)

Proposed Age group: Adults \geq 18.

Pharmacologic Class: Proton Pump Inhibitor

Route of administration, Description, and Formulation: Delayed-release granule for oral administration with applesauce, apple juice, and with apple juice through a nasogastric tube

Proposed Treatment Regimen: 40 mg once daily.

2.2 Currently Available Treatment for Indications

Five proton pump inhibitors are marketed in the United States {Rabeprazole, Pantoprazole, Lansoprazole, Omeprazole and Esomeprazole}. Two of these, lansoprazole and esomeprazole, are available as a delayed-release granules formulation.

2.3 Availability of Proposed Active Ingredient in the United States

Pantoprazole sodium is available in the United States.

2.4 Presubmission Regulatory Activity

IND 68,011 was submitted for pantoprazole spheroid (granules) formulation on August 23, 2003 for oral administration for the treatment of gastroesophageal reflux disease (GERD).

Protonix delayed-release tablets (NDA 20-987) were 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 (IND 68,011, SN 0014), the sponsor requested a Type C meeting with the FDA, and sent a meeting background package detailing a pharmacodynamic (PD) equivalence

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approach to bridge the commercial pantoprazole sodium delayed-release granules and 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. Based on the FDA responses to the questions in the background package, the sponsor cancelled the Type C meeting and proceeded with the development plan.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No CMC issues have been identified. The active drug substance is pantoprazole sodium sesquihydrate, the same drug substance that is used in Protonix Delayed-Release tablets, which is approved under NDA 20-987. It will be obtained from the same suppliers, and will conform to the same specifications as approved in NDA 20-987.

3.2 Animal Pharmacology/Toxicology

For a preclinical standpoint, the NDA application is approvable, and no changes in the preclinical section of the currently approved label are recommended.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data were supplied from the

Inspectors from the DSI division of the FDA conducted audits of both facilities. No violations were seen at However, numerous faults were found at the facility. Among these were:

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- Failure to demonstrate the performance of the assay for titratable acid in gastric aspirates.
- Failure to retain records of laboratory operations performed for validation and testing.
- Acceptance of data outside the specified acceptance limits
- Failure of the analyst to sign and date original data entries on the day of acquisition

Medical Officer's Comments:

These deficiencies render the data obtained at this facility invalid.

4.2 Tables of Clinical Studies

Table 1
NDA 22,020
Tabular Listing of Clinical Studies

Protocol No.	Design	Drug/Dose	Frequency	No.	Sex, Race	Age
3001A1 -118-US	Randomized, open-label, 3-period, 6-sequence crossover, inpatient study in healthy subjects 7-day/6-night treatment period.	Pantoprazole delayed-release granules 40 mg under fasted or fed condition 30 or 60 minutes before standard high-fat breakfast	Pantoprazole delayed-release granules orally on study day 1 of each study period	25	24 M 14 B 9 W 1 other	18 - 45
3001B1 -332-US	Multiple-dose, randomized, open-label, 2-period, 2-sequence crossover study in subjects with GERD and history of EE comparing 40-mg of pantoprazole sodium delayed release granules and delayed-release tablet.	Period 1: pantoprazole sodium granules 40 mg; tablet 40mg Period 2: pantoprazole tablet 40 mg; granules 40 mg	Pantoprazole granules 40 mg: sprinkled on applesauce once daily ½ hour before breakfast	38	21M 17F 25W 1B 12 Other	21-63
			Pantoprazole tablet 40 mg: once daily ½ hour before breakfast	38		26-64

4.3 Review Strategy

As noted, five clinical studies were conducted to support the development of pantoprazole delayed-release granules. The studies were conducted to support the use of pantoprazole granules as an alternative to the marketed Protonix tablets for adult patients who are unable to swallow tablets. Pivotal study 3001B1-332-US was performed to demonstrate the pharmacodynamic comparability of the granule formulation to the marketed tablet formulation. Results of all studies are included in the current submission, and have been reviewed as part of the NDA.

Medical Officer's Comments:

As noted, this review will focus on the Phase 3 PD and safety study 3001B1-332-US, with reference to other studies as needed.

4.4 Data Quality and Integrity

Medical Officer's Comment:

As noted, data quality from [] [] unacceptable.

4.5 Compliance with Good Clinical Practices

According to the sponsor, the clinical study was conducted according to Good Clinical Practice (GCP) guidelines, as documented in the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA).

4.6 Financial Disclosures

The sponsor has submitted form 3454, certifying that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study, as defined in 21 CFR 54.2(a).

Medical Officer's Comments:

The sponsor has certified that they did not enter into any financial agreement with the clinical investigators whereby the value of their compensation could be affected by the outcome of the studies.

5 CLINICAL PHARMACOLOGY

A separate and full review is submitted by the Clinical Pharmacology reviewer.

5.1 Pharmacokinetics

Study protocol 3001B1-116-US (CSR-61354) was entitled "*An open-label, randomized, 3-period, crossover, bioequivalence study of the to-be-marketed formulation of pantoprazole sodium enteric coated spheroids administered in 3 dose regimens to healthy subjects.*" This was an open-label, single-dose, randomized, 3 period, 6 sequence crossover, inpatient study. Of the 25 subjects enrolled, 25 completed the study. Pantoprazole delayed-release granules, 40 mg, were sprinkled over applesauce (regimen A), mixed with apple juice (regimen B), or mixed with apple juice and administered through an NG tube (regimen C).

Pharmacokinetic results demonstrate that the mean C_{max} and AUC for the delayed release granules administered in apple juice and through a NG tube are similar to those administered in apple sauce. The table 2 provides a summary of these PK parameters:

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Table 2 NDA 22, 020 Study 3001B1-116-US Summary of Pharmacokinetic Parameters for Pantoprazole Granules					
Regimen	C _{max}	t _{lag}	t _{max}	AUC _T	AUC
Granules in applesauce (GAS)	1969 ± 690	0.50	2.0	3973± 1526	4008± 1529
Granules in apple juice (GAJ)	1913± 447	0.50	2.5	3936± 1485	3985± 1486
Granules in NG tube (GNG)	2182 ± 697	1.0	2.0	4029± 1721	4063 ± 1725
Geometric Mean Ratio (GAJ)	101.97	----	----	100.05	100.42
Geometric Mean Ratio (GNG)	113.39	----	----	99.96	99.94
90% CI (GAJ)	92.4 - 112.5	----	----	94.4 - 106.1	94.8 - 106.4
90% CI (GNG)	102.7 - 125.2	----	----	94.3 - 106.0	94.3 - 105.9

Medical Officer's Comments:

C_{max} and AUC show bioequivalence between the granules in applesauce, apple juice and granules in apple juice administered through a nasogastric tube. Of note, bioequivalence between pantoprazole tablets and granules was not demonstrated.

5.2 Pharmacodynamics

A key element of the clinical development program supporting this NDA was the demonstration of pharmacodynamic (PD) comparability between the granules tablet formulations. The primary endpoint of pentagastrin stimulated maximum acid output (PG-MAO) at a steady state, was used to bridge the proposed granules to the marketed tablet

PG-MAO was assessed from hour 23 to 24 at steady state in a multicenter pharmacodynamic crossover study (3001B1-332-US) in subjects with GERD and a history of EE. The results of this study demonstrate that the granules were comparable to the tablet in suppression of acid in these patients. The maximum acid output (MAO) for the two formulations of 40 mg pantoprazole was comparable for the modified intent-to-treat (mITT) population analyzed in this study, with an overall mean MAO and standard deviation for all subjects of 7.11 ± 4.98 mEq/h, and 7.29 ± 4.77 mEq/h, for the granule formulation and the tablet formulation, respectively.

Medical Officer's Comments:

The sponsor has submitted data demonstrating PD comparability between the delayed-release tablet and the delayed-release granules. However the assay used to conduct PD comparability testing was in violation of the protocol. Consequently, PD comparability between the two formulations cannot be determined.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The manufacturers of pantoprazole granules are seeking approval for the same indications for which pantoprazole tablets are approved; short-term treatment of patients with GERD and a history of EE; maintenance of healing of EE; and long-term treatment of pathological hypersecretory conditions.

6.1.1 Methods

With valid bioequivalence and/or PD comparability studies, the efficacy of pantoprazole granules would be based on clinical data obtained from pantoprazole tablets. Hence no efficacy trials were conducted with the pantoprazole granules since the sponsor aimed to establish efficacy based on a finding of PD comparability between pantoprazole delayed-release granules and pantoprazole delayed-release tablets.

The most frequently tested dosage regimen in clinical trials of pantoprazole in subjects with GERD has been 40-mg tablets administered once daily. Data have shown that this dosage produces efficient inhibition of gastric acid secretion accompanied by only moderate increases in serum gastrin levels in humans.

6.1.2 General Discussion of Endpoints

The primary endpoint of study 3001B1-332-US was pentagastrin-stimulated MAO after administration of a 40-mg dose of each formulation (delayed-release granules and delayed-release tablets) once daily for one week during each period. MAO was the average of four 15 minute collections.

Secondary endpoints included a description of the steady-state profiles of several additional PD endpoints: BAO; integrated gastric acidity; mean and median intragastric pH; mean and median intraesophageal pH; percentage of time that intragastric pH was >3 and percentage of time that intragastric pH was >4; percentage of time that intraesophageal pH was <4; number of reflux episodes; number of reflux episodes longer than 5 minutes; and duration of the longest reflux episode.

Medical Officer's Comment:

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., C_{max}) cannot be obtained.

6.1.3 Study Design

STUDY 3001B1-332-US:

Protocol 3001B1-332-US was a multiple-dose, randomized, open-label, 2-period, 2-sequence crossover study in subjects with GERD and a history of EE comparing a 40-mg dose of pantoprazole sodium delayed-release granule and the currently marketed pantoprazole sodium delayed release 40-mg tablet.

Subjects participated in the study for approximately 9 weeks. This period consisted of a screening evaluation, conducted within the 21 days before test article administration, a clinical period of approximately 30 days (two one-week treatment phases separated by a washout period of 14 to 21 days), and a follow-up telephone assessment 12 to 18 days after the last dose of study medication. Routine safety evaluations were performed from spontaneously reported adverse events (AEs), scheduled physical examinations, vital sign measurements, and clinical laboratory test results. The following table depicts the study procedures during each period.

**Table 3
 NDA 22,020
 Protocol 3001B1-332-US
 Overall Study Flowchart**

Visit ID	Screening		Treatment Period 1		Washout	Treatment Period 2		Follow-up ²
	Days -21 to -8	Days -7 to -3	Day 1	Days 6-8	14 to 21 days	Day 1	Days 6-8	12 to 18 days
Study Procedures:								
Informed consent	X							
Assess inclusion/exclusion criteria	X		X					
Demographics/medical history ¹	X							
Physical examination	X		X			X	X	
Vital signs ²	X		X	X		X	X	
12-lead electrocardiogram	X							
Hematology/chemistry/urinalysis	X		X	X		X	X	
Urine drug screen	X							
Urine pregnancy test (women)	X		X			X	X ²	
<i>Helicobacter pylori</i> test	X	X ²	X					
Fasting serum gastrin	X	X ²						
Dispense Gélusil, diary card	X		X	X		X		
Gélusil/test article accountability			X	X		X	X	
Inpatient stay				X			X	
Pharmacodynamic assessments				X			X	
Randomization			X					
Test article administration			X	X		X	X	
Prior, concomitant medications	X							X
Adverse events	X							X

The study contained a washout period of 14 to 21 days, during which no study assessments were made. A follow-up visit was conducted by telephone 12 to 18 days after the final evaluation to record and assess any AEs and concomitant medications used since the last assessment.

Medical Officer's Comment:

As shown in the above flowchart, PD assessments were to have been obtained on day 7 by insertion of a pH probe, and day 8 after pentagastrin stimulation. These PD assessments were

intended to provide the basis for study 3001B1-332-US, which aimed to demonstrate PD comparability between the granules and tablet formulations.

STUDY 3001-B1-116-US:

Protocol 3001-B1-116-US was an open-label, single-dose, randomized, 3-period, 6-sequence crossover, inpatient study conducted at a single investigative site. The study was designed to establish bioequivalence between the 3 proposed methods for administration of the granules. Doses were administered after an overnight fast of at least 10 hours. Healthy men and women of non-childbearing potential aged 18 to 50 years were eligible for enrollment if all other qualifying criteria were met. A flowchart of assessments is shown below:

Table 4
NDA 22,020
Study 3001B1-116-US
Study Flowchart

Study Procedure	Screening ^a	Period 1		Period 2		Period 3		Final Study Evaluation	
Dose Days	-21 to -2	-1	1	2	1	2	1	2	
Study Days	-21 to -2	-1	1	2	3	4	5	6	
Informed consent	X								X
Outpatient visit	X								
Inpatient confinement		X							X
Medical history	X								
Physical examination	X ^b	X ^d							X ^d
Vital signs ^c	X	X	X	X	X	X	X	X	X
12-Lead electrocardiogram	X	X	X	X	X	X	X	X	X
Laboratory evaluation ^e	X	X	X	X	X	X	X	X	X
Blood sample for possible future pharmacogenomic analysis		X							
Pregnancy test for women (β-HCG)	X	X							X
Urine drug screen	X	X							
HbsAg, HCV, HIV antibody screen	X								
Test article administration			X		X		X		
Blood samples for pharmacokinetics			X	X	X	X	X	X	
Adverse event monitoring	X								X
CPE number (for sponsor use only)	1	2	3/4	5	6/7	8	9/10	11	12

In this study each subject received a single 40 mg dose of pantoprazole under fasting conditions in 3 regimens, A, B, and C, as defined below. Each dose was separated by a washout interval of at least 1 day. Subjects were randomly assigned to 1 of 6 of the following treatment sequences: ABC, BCA, CBA, ACB, BAC, CAB:

- A: pantoprazole granules sprinkled over applesauce
- B: pantoprazole granules in apple juice
- C: pantoprazole granules in apple juice, administered through an NG tube

Blood samples were collected for determination of pantoprazole concentrations at the following times: on study day 1, predose (time 0) collected within 2 hours before test article administration and at 0.33, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after test article administration.

6.1.4 Efficacy Findings

In study 3001-B1-332-US, pentagastrin-stimulated MAO from hour 23 to 24 at steady state, defined as the 24-hour period starting at the time of administration of the seventh dose of pantoprazole, was the primary PD variable. The primary comparison between the two formulations was based on testing the null hypothesis that the MAO after the last granule (formerly spheroid) dose (MAO_{spheroid}) would be more than 20% higher than the MAO after the last tablet dose (MAO_{tablet}), against the alternative hypothesis that the MAO after the last granule dose (MAO_{spheroid}) would be less than 20% higher than the MAO after the last tablet dose (MAO_{tablet}).

The overall mean MAO and standard deviation for all subjects are 7.11±4.98 mEq/h and 7.29±4.77 mEq/h for the granule formulation and the tablet formulation, respectively.

Table 5
Study 3001B1-332-US
NDA 22,020

Summary Statistics for Maximum Acid Output (mEq/h) by Formulation, Modified ITT 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

These results demonstrate that the maximum acid output for the granule formulation was at most 20% greater than that of the tablet formulation and therefore, the 2 formulations of pantoprazole were comparable for the mITT population.

Medical Officer's Comments:

As noted, efficacy was not the purpose of the study. The results submitted by the sponsor show that both formulations are able to inhibit PG-MAO in a comparable fashion, thus demonstrating pharmacodynamic comparability.

6.1.5 Efficacy Conclusions

- 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.

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- 332-008-0118 nausea day 6 period one, tablet formulation.

Medical Officer's Comment:

In Study 3001B1-114-US two Hispanic males showed an increase in CPK likely due to muscle breakdown from exercise. In Study 3001B1-332-US none of the adverse events associated with subject discontinuations were serious (SAEs), or related to the study medication.

7.1.3.1 Overall profile of dropouts

As noted, two dropouts were healthy volunteers with elevated CK levels at baseline, who experienced an increase in CK levels after receiving the study medication. The other four were patients with GERD, whose AEs did not appear to be study-related.

Medical Officer's Comments:

The elevations in CK were non-specific, and likely caused by muscle injury during exercise or strenuous activity. Of note, the current label lists elevation of CPK as a musculoskeletal injury seen in post-marketing reports.

7.1.3.2 Other significant adverse events

As discussed above, one GERD patient in study 3001B1-332-US experienced an elevation in CK and seven healthy volunteers in study 3001A1-114-US had CK elevations. Most of these subjects were Hispanic males with mildly elevated baseline CK values. Two subjects with elevated CK were withdrawn from the study. The peak plasma concentrations for pantoprazole for the two withdrawn subjects (008 and 0010) were similar to those observed for the other subjects in the study.

Subject No.	Age	Sex	Race	Baseline Elevated CK	CK Max	Withdrawn	Additional Information
114001-005	33.3	M	Hispanic	No	791	No	moving furniture
114001-006	29.8	M	Hispanic	272	801	no	
114001-008	34.8	M	Hispanic	657	18,747	Yes	
114001-0010	38.5	M	Hispanic	220	697	Yes	
114001-0012	28.9	M	White	No	237	No	
114001-0015	26.6	M	Hispanic	271	368	No	
114001-0023	27.8	F	Black	No	519	No	
332007-0112*	33	M	Hispanic	No	26,085	No	

*CK elevated days 1 to 8 period 2 following 14 day washout. Subject began weightlifting program during washout period.

Because of the occurrences of CPK elevations in studies 3001A1-114-US and 3001B1-332-US, a cumulative review, through 06 Mar 2006, of all cases of increased CPK and/or rhabdomyolysis coincident with pantoprazole therapy available in the Safety Surveillance System (S₃), the GSSE

Medical Officer's Comments:

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

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data was obtained from 5 clinical studies conducted either with the pilot formulation or the granules formulation in 185 healthy subjects or patients with GERD and a history of EE. Data from postmarketing safety reports since the approval of Protonix® through 01 Feb 2006 was also considered.

The safety results from the clinical studies of healthy subjects (3001B1-116-US, 3001A1-114-US, 3001A1-115-US, and 3001A1-118-US) and subjects with GERD (3001B1-332-US), demonstrate that the delayed-release granules are safe and well tolerated.

In study 3001-B1-332-US the rate of treatment emergent adverse events (TEAEs) experienced by subjects treated with granules was similar to that observed with the tablet formulation. Likewise the safety results from clinical studies of healthy subjects and subjects with GERD show that the granules are safe and well-tolerated. Most adverse events were of mild to moderate intensity, and unrelated to the study medication.

Elevated creatine phosphokinase (CPK) was reported as a TEAE in one subject in the granules treatment group of study 3001B1-332-US and seven subjects in study 3001A1-114-US (4 treated with granules suspension and 3 treated with pantoprazole delayed release tablet). Seven of the 8 cases of CPK elevations were designated as TEAEs and 1 (in study 3001A1-114-US) was considered to be a serious adverse event. Two of the 8 subjects discontinued from the study (3001A1-114-US) prematurely because of elevated CPK.

Headache was the most common TEAE for both formulations. Nausea and dizziness were the most common pentagastrin-related TEAE.

Medical Officer's Comments:

Elevated CPK is discussed later in this review. Subjects experiencing CPK elevations were young active males, and may have developed CPK elevation due to strenuous physical activity. Other AE findings were not unexpected, or inconsistent with the known safety profile of pantoprazole.

7.1.1 Deaths

No subjects died while participating in studies conducted with pantoprazole granules or tablet.

7.1.2 Other Serious Adverse Events

There were no serious or potentially serious adverse events noted in studies 3001B1-332-US , 3001B1-116-US, 3001A1-115-US or 3001A1-118-US. In study 3001A1-114-US, one subject (114-001-008) had elevations in CPK, AST and ALT values. Although the rise in CPK may have been related to physical activity rather than pantoprazole, the subject was withdrawn from the study. Overall, elevated creatinine phosphokinase was the only adverse event that that appeared to be clinically important in any of the five studies reviewed in this NDA.

7.1.3 Dropouts and Other Significant Adverse Events

Studies 3001B1-116-US, 3001B1-115-US, and 3001B1-118-US did not report dropouts or premature discontinuations. In study 3001A1-114-US, shown below in Table 5, two subjects withdrew due to AEs. Both had increases in creatinine phosphokinase (CPK) from baseline levels (also elevated).

Table 6
NDA 22,020
Subject withdrawn from Study 3001A1-114-US

Subject/Study day	Demographic	Reason with Withdrawal	Comments	Formulation
114-001-008/7	34 yr. Hispanic male	increase in CPK (CPK elevated at baseline)	ECG normal exercising	tablet
114-001-0010/5	38 yr. Hispanic male	increase in CPK (CPK elevated at baseline)	ECG normal	granules

As shown in table 6, adverse events were a cause of four withdrawals in study 3001-B1-332-US .

Table 7
NDA 22,202
Protocol 3001-B1-332-US
Listing of Subject Discontinuations With Adverse Events as Primary Reason

Subject	Treatment Sequence	Study Day	Conclusion Reason	AE Preferred Term	Conclusion Date
332-002-0023	Tablet 40 mg/ Spheroid 40 mg	7	Adverse event	Headache	23 Jul 2005
			Adverse event	Nausea	23 Jul 2005
			Adverse event	Vomiting	23 Jul 2005
332-005-0080	Spheroid 40 mg/ Tablet 40 mg	49	Adverse event	Upper respiratory infection	07 Oct 2005
332-007-0101	Tablet 40 mg/ Spheroid 40 mg	25	Adverse event	Rhinitis	01 Sep 2005
332-008-0118	Tablet 40 mg/ Spheroid 40 mg	21	Adverse event	Nausea	21 Sep 2005

- 332-005-0023 headache, nausea, vomiting day 7 period 1 treatment with tablet
- 332-005-0080 upper respiratory tract infection on relative day 29 during washout.
- 332-007-0101 nasal congestion day 8 period one, 1 day after final treatment with the tablet formulation.

database was performed by sponsor. The GSSE database (S3) contains serious and non-serious spontaneous reports for Wyeth products that are obtained from marketed AEs, both foreign and domestic, from consumers, health care professionals, registries, licensing partners, and literature reports. Additionally, the S3 database contains SAE reports from investigational studies conducted by Wyeth Clinical CR&D, ALTANA Pharma and from non-CR&D post-marketing studies, regardless of causality of the AE.

The results of the search of the S3 database, the clinical cases in the trials that support this submission, and a review of the cases reported in the literature suggest a reasonable suspicion that therapy with pantoprazole appears to be associated with very rare reports of elevated blood CPK levels, and/or rhabdomyolysis. Given the rarity of the reports of elevated CPK and/or rhabdomyolysis coincident with pantoprazole therapy, the sponsor considers the current labeling to be sufficient. Therefore, no changes regarding CPK elevations are proposed in the pantoprazole delayed-release granule labeling. The sponsor will continue to monitor future cases of elevated CPK and rhabdomyolysis coincident with the administration of pantoprazole.

Medical Officer's Comment:

Increased CK levels have been reported with pantoprazole, and are already noted in the current label. The seven subjects reported in table 7 were mostly young physically active male subjects. The sponsor's approach is adequate.

7.1.4 Common Adverse Events

7.1.4.1 Incidence of common adverse events

Subjects with GERD – Study 3001B1-332-US:

The most common AEs ($\geq 5\%$) with pantoprazole treatment (both formulations) were headache and vomiting. Headache was experienced by 5 (7%) of subjects taking granules and 4 (6%) in the tablet formulation. There were no statistically significant differences between the granule and tablet formulations for any body system or AE.

Medical Officer's Comment:

The incidence of adverse events seen with pantoprazole delayed-release granules was similar to those seen with pantoprazole delayed-release tablets.

7.1.5 Laboratory Findings

In GERD patients (3001B1-332-US), no statistically significant differences in laboratory test results of potential clinical importance between treatments were identified.

For 3 subjects, including subject 0020, (neutrophils: screening 44% decreased to 41.3%), subject 0018 (phosphorus: 5.2 mg/dL on day 1 after study drug administration), and subject 0012 (low neutrophils: 35.6% on day 1 prior to study drug increased to 43.2% on day 1 after study drug

administration), results for the laboratory parameter were consistently outside the normal range from screening or day-1 and reached levels of potential concern during the study.

Medical Officer's Comments:

These laboratory abnormalities, with the exception of CK, were noted at baseline, and were not significantly exacerbated by administration of the study drug.

7.1.6 Vital Signs

In protocols involving GERD patients, and healthy volunteers, there were no statistically significant differences in vital signs of potential clinical importance between treatments.

7.1.7 Electrocardiograms (ECGs)

STUDY 3001B1-332-US:

Electrocardiograms were done at screening, but were not a part of the ongoing safety assessments for protocol 3001-B1-332-US. Patients with ECG abnormalities were excluded from the study by virtue of the exclusion and inclusion criteria.

- **Inclusion Criteria:** (not comprehensive)

Subjects were to have clinical laboratory values within the normal limits for the central laboratory and **normal results for a 12-lead ECG**, unless the investigator documented that the deviations were not clinically significant or were directly related to an allowable preexisting condition.

- **Exclusion Criteria:** (not comprehensive)

Unstable cardiovascular, pulmonary, or endocrine disease; clinically significant renal or hepatic disease or dysfunction; hematologic, neurologic and psychiatric disorder; any clinically significant medication condition, including malignancy, except for successfully resected basal cell skin cancer, that could increase the risk to the study participants. Certain subjects with chronic stable medical conditions (e.g., mild renal or hepatic dysfunction, essential hypertension) were to be permitted into the study on a case-by-case basis with prior approval of the WR medical monitor.

Medical Officer's Comment:

Cardiovascular abnormalities and arrhythmias, including an increase in the QT interval, are not among the common adverse reactions to the PPI class of drugs. Hence lack of ECG monitoring during the study period is not problematic. A screening ECG would have identified (and excluded) patients with abnormal electrocardiograms at baseline.

STUDY 3001B1-116-US:

Twelve-lead ECGs were performed at screening; on study day -1 of study period 1; on study day 1 within 2 hours of dose administration and at 1.5 hours after dose administration of study periods 1, 2, and 3; and the final study evaluation.

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Twelve-lead ECGs were performed at 25 mm/s at scheduled intervals. The investigator was responsible for providing the interpretation of all ECGs. The results included heart rate, rhythm, PR, QRS, QT, and QTc intervals.

Increased PR intervals were recorded for 3 subjects. Before receiving pantoprazole, subject 0017 had an increased PR interval of 266 msec predose in period 1 and 268 msec predose in period 3 (234 msec at screening) and subject 0018 had an increased PR interval of 222 msec predose in period 2 (164 msec at screening). Subject 0014 had an increased PR interval of 220 msec 1.5 hours after dosing in period 1 (174 msec at screening). Low heart rate was recorded for 2 subjects. Subject 0004 had a low pulse 2 hours before dosing in period 2 (44 bpm compared to 79 bpm at screening). Subject 0011 had a low pulse in period 3, 2 hours predose and 1.5 hours post dose (45 bpm both times, 64 bpm at screening). All other ECG values were within normal limits for these subjects and all other subjects.

Medical Officer's Comment:
No QTc abnormalities are noted.

7.1.8 Postmarketing Experience

N/A

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

In protocol 3001B1-332-US, 76 subjects with GERD and a history of EE were exposed to a daily dose of the 40 mg tablet or 40 mg granules for 1 week with a 14- to 21-day washout period between treatments. Approximately 87% of subjects completed the oral dose schedule (a 40 mg dose once daily for 1 week) for the granule formulation. Approximately 88% of subjects completed the oral dosing schedule (40 mg dose once daily for 1 week) for the tablet formulation. Patients were monitored for adverse events. No subject's ≥ 65 years old were enrolled.

In protocol 3001B1-116-US, all 25 subjects completed dosing during the 3 treatment periods that included 40 mg of pantoprazole granules administered with apple juice, sprinkled on applesauce and mixed with apple juice and administered through an NG tube. Each subject received a single 40-mg dose of pantoprazole granules under fasting conditions in each of 3 treatment periods.

In protocol 3001A1-114-US, 24 of 26 (92.3%) subjects completed all 3 treatment periods in which 3 doses of 40-mg of pantoprazole were administered on day 1 as a tablet, granules sprinkled on applesauce, or granules as a suspension. Two (2) subjects were withdrawn from the

study after receiving 2 doses; they did not receive a dose of pantoprazole in period 3. The 2 replacement subjects did complete all 3 periods of the study.

In protocol 3001A1-115-US, all 34 subjects completed dosing with 40 mg of pantoprazole granules under fasted/fed or fed/fasted conditions. Seventeen (17) subjects received pantoprazole granules in applesauce, 8 under fasted/fed conditions and 9 under fed/fasted conditions. Seventeen (17) additional subjects received pantoprazole granules mixed with apple juice, 8 under fasted/fed conditions and 9 under fed/fasted conditions.

In protocol 3001A1-118-US, all 24 subjects completed 3 single doses with 40 mg of pantoprazole granules as a suspension after fasting and 30 and 60 minutes before a high-fat breakfast.

Medical Officer's Comment:

The overall patient exposure and safety assessments are adequate.

7.2.1.1 Study type and design/patient enumeration

One study evaluated patients with GERD, and four studies looked at healthy volunteers. Protocol 3001B1-332-US was a Phase 3, multiple-dose, randomized, open-label, 2-period, 2-sequence crossover study in subjects with GERD and a history of EE which compared a 40-mg dose of pantoprazole sodium delayed-release granule to the currently marketed pantoprazole sodium delayed release 40-mg tablet.

Study, 3001B1-116-US was a Phase 1, open-label, single-dose, randomized, 3-period, 6-sequence crossover, inpatient study conducted at a single investigative site. Doses were administered after an overnight fast of at least 10 hours. Healthy men and women of non-childbearing potential aged 18 to 50 years were eligible for enrollment if all other qualifying criteria were met.

Studies 3001B1-114-US, 3001B1-115-US, and 3001B1-118-US were bioavailability studies on healthy volunteers using a pilot granules formulation.

7.2.1.2 Demographics

A total of 76 patients were enrolled in the PD equivalence study. The following table provides a description of selected demographic characteristics of the safety population.

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Table 9
NDA 22,020

Demographic and Baseline Characteristics. Safety Population			
Characteristic	Spheroid/Tablet	Tablet/Spheroid	Total
Mean Age	45.5	42.74	44.12
Sex, female	17 (44.74)	17 (44.74)	34 (44.74)
male	21 (55.26)	21 (55.26)	42 (55.26)
Race, Asian	2 (5.26)		2 (2.63)
Black	1 (2.63)	1 (2.63)	2 (2.63)
Other	8 (21.05)	4 (10.53)	12 (15.79)
White	25 (65.79)	33 (86.42)	58 (76.32)

Medical Officer's Comments:

The study population was fairly well balanced by sex, but not well balanced by race. No patient was over the age of 65.

7.2.1.3 Extent of exposure (dose/duration)

Approximately 87% of subjects completed the oral dose schedule (a 40 mg dose once daily for 1 week) for the granule formulation. Approximately 88% of subjects completed the oral dosing schedule (40 mg dose once daily for 1 week) for the tablet formulation. Patients were monitored extensively for adverse events (see Table 2).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical data sources were used to evaluate safety.

7.2.3 Additional Submissions, Including Safety Update

During the review period for NDA [] the sponsor submitted the 23rd period safety update, covering the period from Aug. 24, 2005 to Feb. 23, 2006. The Periodic Safety Update Report (PSUR) summarizes the safety data obtained and assessed by the Corporate Drug Safety Department at ALTANA Pharma AG (ALTANA) from worldwide sources for the above-mentioned reporting period in the format described in the ICH E2C Guideline. The sponsor notes that an estimated [] patients were treated with pantoprazole-sodium tablets. The number was [] higher than during the previous report period. An estimated number of [] patients received pantoprazole intravenously, which was [] higher than in the previous report period.

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Overall, 605 case reports on pantoprazole-sodium were finally evaluated. 496 of these were spontaneous reports, involving 165 serious cases. All in all, 126 cases contained 227 serious and unlisted symptoms. Three of these 227 symptoms were assessed as possibly related, one as likely, none as definitely related by the Corporate Drug Safety Department of ALTANA. The

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sponsor concludes that the post marketing surveillance during this report period does not reveal new safety concerns with impact on the well-established overall safety profile of the product.

Medical Officer's Comments:

The 23rd Periodic Safety Update provides results of further close monitoring for rhabdomyolysis. For the period covered by this update, 4 cases of rhabdomyolysis were reported, with 2 deemed not evaluable, and 2 unlikely. The safety of pantoprazole will continue to be evaluated in future updates.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Both formulations of pantoprazole were shown to be safe and well tolerated. The rate of occurrence of TEAEs was similar between the pantoprazole tablets and granules. Headache was the most common reported non-pentagastrin-related TEAE for both formulations. Nausea and dizziness were the most common reported pentagastrin-related TEAEs. No deaths or SAEs were reported. Four (4) subjects were withdrawn from study 3001-B1-332 due to adverse events.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Pantoprazole delayed-release are available in unit dose Each contains enteric-coated granules containing 45.1 mg pantoprazole sodium sesquihydrate (equivalent to 40 mg pantoprazole). The recommended adult oral dose of the granules was to have been the same as the approved dose for the tablet formulation, for each indication.

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8.2 Drug-Drug Interactions

N/A

8.3 Special Populations

N/A

8.4 Pediatrics

N/A

9 OVERALL ASSESSMENT

9.1 Conclusions

The current NDA seeks approval of pantoprazole sodium delayed-release granules oral formulation as an alternative to the marketed tablet formulation for patients who are unable to swallow the tablet. The key element of the clinical development program supporting this NDA was to have been the pharmacodynamic comparability study designed to bridge the proposed granules formulation to the marketed tablet formulation. No efficacy trials were conducted with the pantoprazole sodium delayed-release granules.

Extensive safety and efficacy data for the use of oral and I.V. pantoprazole sodium for the treatment of gastroesophageal reflux disease and other gastric acid-related disorders have been obtained from over 200 clinical studies worldwide. Also, both oral and I.V. administration of pantoprazole have been shown to be effective in reducing intragastric acid output in clinical studies.

The pharmacodynamic comparability approach was previously used in study 3001K1-309-US (GMR-32141) in support of the registration application for intravenous use of pantoprazole sodium for treatment of patients having GERD with a history of EE, as an alternative to oral therapy in patients who are unable to continue taking pantoprazole sodium delayed-release tablets. This data was submitted in the 20 July 1998 NDA 20-988. The results of study 3001K1-309-US demonstrated the pharmacodynamic comparability of the I.V. formulation to the tablet formulation, and provided the basis for the approval of the proposed use of the I.V. formulation. A similar approach was also used to support the initial use of the I.V. formulation (NDA 20-988/S-027).

In the current submission, a pharmacodynamic comparability approach was also utilized. However, due to irregularities identified during a DSI audit, the PD results are not valid, and cannot be used in support of this NDA.

9.2 Recommendation on Regulatory Action

Approval of this application is not recommended.

The sponsor has submitted data from 5 studies. Three (studies 3001A1-114-US, 3001A1-115-US and 3001A1-118-US) were pilot studies conducted to examine certain PK characteristics of an early version of pantoprazole sodium delayed-release granule formulation under various conditions, and assist in its development. The other 2 clinical studies (3001B1-332-US and 3001B1-116-US) were the pivotal studies conducted using the to be-marketed delayed-release granules formulation. They were conducted to support the use of the granules formulation as an alternative to the marketed pantoprazole product, for patients are unable to swallow the tablet. Study 3001B1-332-US examined the pharmacodynamic comparability of the granules

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formulation to the marketed tablet formulation. Study 3001B1-116-US showed bioequivalence among the 3 proposed methods for administration of the granules.

Because of irregularities associated with the data for protocol 3001B1-332-US, the results of this study cannot be used for approval of the NDA. Further, the sponsor has not been able to establish bioequivalence between pantoprazole granules and pantoprazole tablet.

9.3 Recommendation on Postmarketing Actions

N/A

9.3.1 Risk Management Activity

N/A

9.3.2 Required Phase 4 Commitments

N/A

9.4 Labeling Review

N/A

9.5 Comments to Applicant

N/A

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10 APPENDICES

10.1 Review of Individual Study Reports

N/A

10.2 Line-by-Line Labeling Review

N/A

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REFERENCES

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