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RESEARCH**

APPLICATION NUMBER:

22-020

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA Number	22-020 (0011)
Letter Date(s)	August 2 nd , 2007 and November 5 th , 2007
Brand Name (Proposed)	Protonix [®]
Generic Name	Pantoprazole Sodium
Reviewer	Abimbola Adebawale, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3 (DCP3)
OND Division	HFD-180
Applicant	Wyeth Pharmaceuticals, Philadelphia, PA
Related IND(s)	68,011
Submission Type	Complete Response to an Approvable Letter
Formulation,; Strength (s)	Delayed-Release Granules (40 mg)
Pharmacological Class	Proton Pump Inhibitor
Indication	Short-term treatment of gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE), maintenance of healing of EE, and long-term treatment of pathological hypersecretory conditions in adults \geq 18 years old.
Reference Listed Drug (RLD)	Protonix [®] Delayed-Release 40 mg Tablets

Table of Contents

1	Executive Summary	1
1.1	Recommendation.....	2
1.2	Phase IV Commitment	2
1.3	Summary of CPB Findings.....	2
2	QBR.....	4
3	Labeling Recommendations.....	12
4	Appendix	17

1 Executive Summary

This amendment is a resubmission for Protonix[®] (pantoprazole sodium) delayed-release oral formulation (equivalent to 40 mg pantoprazole). The purpose of this submission is to provide a complete response to the deficiencies noted in the approvable letter issued by the FDA on March 15th, 2007.

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1.1 Recommendation (s): The information provided in this submission adequately addressed the additional information requested in the FDA written responses received by Wyeth on July 23rd, 2007 to provide a complete response to the deficiencies noted in the Approvable Letter of 15th March, 2007. Therefore, this application is acceptable from a clinical pharmacology perspective. We have labeling recommendations in Section 3.

Comments to be conveyed to the Medical Officer:

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.

In the pharmacodynamic comparability study 3001B1-332-US, although the overall mean \pm SD for MAO from all subjects for the granule formulation and the tablet formulation (7.11 ± 4.98 mEq/h and 7.29 ± 4.77 mEq/h, respectively) appeared similar, the statistical analysis using the one-sided t-test or signed rank test to establish therapeutic comparability was not considered an acceptable approach by the statistics reviewer (Dr. W. Chen). This was because the hypothesis testing applied was a one-sided t-test and not a comparability test (i.e. a 2 one-sided t-test approach).

The unacceptability of this approach was previously conveyed to the applicant during a teleconference held with the FDA on June 23rd, 2005 and it was again conveyed to the applicant on July 20th, 2005. The applicant did not provide a rationale as to why they chose to continue with the one-sided test, but they did indicate in their report that pharmacodynamic comparability was determined for MAO using the same approach in their currently approved IV formulation (NDA # 20-998) in study 3001K1-309-US. On March 12th, 2007, Dr. Welch (Team Leader of Biostatistics) and Dr. Korvick (Deputy Director of GI Division) had discussions via e-mail on the acceptability of this statistical approach. It was decided that numerically the MAO for the granules are similar to those of the tablets and so decisions based on numbers and not strict statistics may be applicable in this case (apparently there is a precedence for this in the GI Division).

1.2 Phase IV Commitments: None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics (CPB) Findings:

Regulatory History:

An FDA approvable letter was issued to the applicant on 15th March, 2007. The deficiencies summarized in the letter were as follows:

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 Pantoprazole Sodium Spheroid 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.

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Prior to the issuance of the approvable letter, Wyeth submitted additional information titled: Response to Establishment Inspection Report (EIR) for Protocol 3001B1-332-US dated 15th March, 2007. A preliminary review of the information on the date of receipt indicated that the DSI inspection concerns with regards to insufficiency in the method validation had not been adequately addressed. Therefore, the approvable letter was issued.

On March 20th, 2007, Wyeth submitted a letter of intent to notify the Agency of their intent to file an amendment to NDA 22-020 to address the deficiencies in the approvable letter, as well as their intent to request a Type A meeting to facilitate resolution of the deficiencies. The purpose of the Type A meeting was to discuss and reach agreement with the Agency on the "complete response" to the approvable letter for NDA 22-020 received from the Agency on 15th March, 2007. Written responses to the questions included in the Wyeth Type A meeting request and information package were faxed by the Agency to Wyeth on July 23rd, 2007. Wyeth was satisfied with the response and thus the meeting did not take place.

The purpose of this submission is to provide a complete response to the deficiencies noted in the approvable letter of 15th March, 2007 through reference to the Type A Meeting request and Information Package and to provide the additional information requested in the FDA written responses received by Wyeth via fax on July 23rd, 2007. Wyeth also requested that labeling negotiations related to NDA 22-020 be conducted in parallel with the Agency's review of this amendment.

Complete Response Summary:

The information provided in this submission adequately addressed the additional information requested in the FDA written responses received by Wyeth on July 23rd, 2007. A summary of the conclusions is as follows:

1. The applicant provided adequate supporting evidence that their 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.

2. The applicant provided an explicit 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 provided consisted of 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).
3. The applicant provided a complete report including the data set for the additional analysis for the primary endpoint, maximum acid output (MAO). In the additional analysis, data from the three additional subjects identified in the FDA, EIR report were excluded. The analysis indicated that the results of the additional analysis are similar to that obtained with the original analysis for study 3001-B1-332-US. Therefore, this findings support the same conclusion that the proposed delayed-release enteric-coated granule formulation 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 Recommendations: Please see section 3 for detailed labeling recommendations.

Signatures:

Abimbola Adebawale, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3, Office of Clinical Pharmacology

Sue-Chih Lee, Ph.D., Team Leader, Division of Clinical Pharmacology 3

2. QBR

2.1 Summary of the CPB findings of the Original Submission

The key element of the clinical development program supporting this NDA was the pharmacodynamic comparability study designed to bridge the proposed granule formulation to the marketed tablet formulation. Therefore, no efficacy trials were conducted with the pantoprazole sodium delayed-release granules. The applicant did not conduct a bioequivalence study between the to-be-marketed granule formulation and the marketed tablet formulation either.

The clinical development program consisted of 5 studies. The 2 pivotal clinical studies (3001B1-332-US and 3001B1-116-US) were conducted using the to-be-marketed pantoprazole sodium delayed-release granules formulation. Study 3001B1-332-US was performed to demonstrate the pharmacodynamic comparability of the to-be-marketed granules formulation to the marketed tablet formulation. Study 3001B1-116-US was carried out to establish bioequivalence among the 3 proposed methods for administration of the granules.

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Study # 3001B1-332-US

The pivotal clinical study # 3001B1-332-US was a multiple-dose, randomized, open-label, 2-period, crossover pharmacodynamic study. This reviewer focused only on the pharmacodynamic assessment of pentagastrin stimulated maximal acid output (MAO). Dr. Nancy Snow (the reviewing medical officer) review dated 2/12/2007 addressed all other aspects of this study. This study was performed to demonstrate the pharmacodynamic comparability of a daily dose of 40mg granules formulation to the 40mg delayed-release tablets in subjects (N=76) with GERD and a history of EE following 1 week of administration. The primary pharmacodynamic measurement was the MAO measured from the 23rd to the 24th hour after the 7th day of administration of either the granule or tablet formulation.

The integrity of this PD comparability data could not be established due to the inadequacy of the analytical method validation submitted which was also confirmed during a DSI audit of the facility where the analysis was conducted. In addition, although the overall mean \pm SD for MAO from all subjects for the granule formulation and the tablet formulation (7.11 ± 4.98 mEq/h and 7.29 ± 4.77 mEq/h, respectively) appeared similar, the statistical analysis using the one-sided t-test or signed rank test to establish therapeutic comparability was not an acceptable approach. The hypothesis testing as proposed is one-sided and not a comparability test (i.e. 2 one-sided t-test approach). The unacceptability of this approach was previously conveyed to the applicant during a teleconference held with the FDA on June 23rd, 2005 and it was again conveyed to the applicant on July 20th, 2005. The applicant did not provide a rationale as to why they chose to continue with the one-sided test, but they did indicate in their report that pharmacodynamic comparability was determined for MAO using the same approach in their currently approved IV formulation (NDA # 20-998) in study 3001K1-309-US. On March 12th, 2007, Dr. Welch (Team Leader of Biostatistics) and Dr. Korvick (Deputy Director of the GI Division) had discussions via e-mail on the acceptability of this statistical approach. It was decided that numerically the MAO for the granules are similar to those of the tablets and so decisions based on numbers and not strict statistics may be applicable in this case. Dr. Korvick stated that GI had approved another drug based on the similarity of numbers and not strict statistics.

Study # 3001B1-116US:

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 when all the subjects were include in the analysis. A summary of the findings is as follows

- For C_{max} , AUC_T , and AUC_{inf} , 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 C_{max} , AUC_T , and AUC_{inf} , 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 (n =25) were included.
- However, the exclusion of 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 C_{max} , AUC_T , 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 %.
- Although exclusion of the 3 subjects resulted in bioequivalence (as shown in the table below), 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 if, adequate precautions are not taking to prevent the clogging of the tube.

Table 1: Summary of Pharmacokinetic Parameters for Pantoprazole Granules (N = 22; 3 subjects excluded)

Regimen ^a	Cmax (ng/mL)	tlag (h)	tmax (h)	AUC _T (ng.h/mL)	AUC (ng.h/mL)
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 ^b (GAJ)	101.97	---	---	100.05	100.42
Geometric mean ratio ^c (GNG)	113.39	---	---	99.96	99.94
90% CI ^b (GAJ)	92.4 – 112.5	---	---	94.4 – 106.1	94.8 – 106.4
90% CI ^c (GNG)	102.7 – 125.2	---	---	94.3 – 106.0	94.3 – 105.9

^a: Values are expressed as mean ± SD, except for tlag and tmax ^b for which medians are reported: Ratio of granules in apple juice to applesauce ^c: Ratio of granules in NG tube to applesauce;

Reviewer's Comments: This information was already conveyed to the medical officer in the original review and labeling recommendations are also provided in Section 3.

2.2 General Clinical Pharmacology and Biopharmaceutics

Q. What does the sponsor's complete response consist of?

In the FDA written responses faxed to the applicant on the 23rd of July, 2007, the Agency concurred with the applicant that a complete response to the FDA approvable letter may consist of the supporting information provided in the Type A Meeting Request and Information Package, in addition to our requests in our responses to Questions 1 and 2.

FDA Written responses Faxed on July 23rd, 2007

FDA Response to Question 1:

To determine the adequacy of your analytical method please provide the following information with your complete response:

- 1) The supporting evidence that your assay method and operating procedures meet the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendment (CLIA) standards.
- 2) An explicit list of all samples that were excluded (due to use of dry ice and mishandled samples) from statistical analysis.

Applicant's Response to Question 1 (#1): the supporting evidence that your assay method and operating procedures meet the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendment (CLIA) standards.

The applicant provided a table listing the various CAP requirements for method validation and a compilation of how those requirements were met in the validation of the assay method used to assess MAO in study 3001-B1-332-US (see table below).

Comparison of CAP Validation Requirements vs. Validation Study:

CAP 2006 Checklist General Checklist - Test Method Validation	Original <input checked="" type="checkbox"/> Validation Study
Precision: GEN.42020-Has the laboratory verified or established and documented analytical precision for each test? Repeat measurement of samples at varying concentrations or activities within-run and between-run over a period of time.	Precision: Within-run: 20 values run and calculated for within run precision. Between-run: 19 values run over 4 runs and interassay precision calculated.
Accuracy-Method Comparison: GEN.42020-Has the laboratory verified or established and documented analytical accuracy for each test? Established by comparison to a definitive or reference method or may be verified by comparing results to an established comparative method.	Accuracy-Method Comparison: The relative accuracy of the method was established by direct comparison of the expected pH buffers to the actual values obtained upon measurement — pH buffers were compared. Linear regression was performed by regular and Deming methods. Ninety five percent confidence limits were used as scatter plot bounds. No outliers were identified. The results yielded a correlation coefficient (r) of 1.000, slope of 1.009, and y-intercept of -0.028.
Analytical Sensitivity: GEN.42025 - Has the laboratory verified or established and documented the analytical sensitivity (lower detection limit) of each assay, as applicable?	Analytical Sensitivity: Determined from the calibration process using multiple buffers. Both zero pH and the slope were determined. Acceptance criteria of <input checked="" type="checkbox"/> was used.
Interfering Substances: GEN.42030 - Has the laboratory verified or established and documented analytical interferences for each test? The laboratory must be aware of common interferences by performing studies or having available studies performed elsewhere (such as the manufacturer).	Interfering Substances: The laboratory was not aware of any interferences in the measurement of gastric acidity by acid titration. Given the large sample pre-dilution factor and that the patients in this study were fasting for 12 hours, their gastric fluid samples consisted of essentially acid and water. No literature reference was found citing any interferences with the measurement of gastric acidity.
Reportable Range (AMR/CRR verification): GEN.42085-Is the reportable range verified/established for each analytical procedure before implementation? AMR=the range of analyte values that a method can directly measure on the specimen without any dilution, concentration or other pretreatment not part of the usual assay process. CRR= range of analyte values that a method can measure, allowing for specimen dilution, concentration or other pretreatment used to extend the direct analytical measurement range.	Reportable Range (AMR/CRR verification): pH linearity verified over a range of <input checked="" type="checkbox"/> Clinical Reportable range established by range of pH standards used. Range not exceeded in study.

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Reference (normal) Range: GEN.42162 - Has the laboratory established or verified its reference intervals (normal values)? Must establish normal ranges where possible for the patient population.	Reference (normal) range: Deemed not applicable for this study involving patient drug treatments.
Records: Commentary: "The laboratory must retain records of method performance specifications while the method is in use and for at least two years after discontinuation of a method."	Records: Validation report kept on file indefinitely.
Accuracy: Spike Recovery: No requirement for spiked recovery.	A spiked recovery was not assessed since no extractions were performed on the gastric aspirates, only 1:10 dilution with water. Accuracy was assessed using certified standards over the entire pH range of interest rather than using the method of standard additions. Excellent correlation between expected and obtained was found.
Selectivity: No requirement for reagent blanks.	The "reagent" blank was, in effect, Type I deionized water (resistivity >10 megohm-cm) and used as the sample diluent. Titration of the 0.1 N HCL showed equivalence with titrated 0.1 N NaOH and demonstrated acceptable precision, <1%. Contribution of the water reagent to overall acidity was shown to be minimal, stable and precise, with no adjustment deemed necessary.
Stability: No requirement for sample stability.	Stability: Refrigeration and frozen stability was assessed over a 30 day period. Samples run in triplicate and assessed for both temperatures on days 3, 7, and 28.

Reviewer's Comments: To ensure that the listing in the table is comprehensive, the applicant also attached the College of American Pathologists (CAP) Laboratory General Check List that cover the assay validation expectations in detail.

The information in the table above indicates that the applicant did not really meet the CAP guidelines for establishing precision for the reference standard acid used. The applicant should have established the precision of the method by including varying concentrations of reference standard acid concentrations to calibrate the titration process. The CAP guidelines states that "Precision is established by repeat measurement of samples at varying concentrations or activities within-run and between-run over a period of time". This is also consistent with the validation method provided in the previous marketing application for the IV infusion in Protocol 3001B1-309-US.

The applicant provided the following information to support the adequacy of their use of one quality control sample to calibrate their titration and establish the precision of the titration method:

1. The applicant stated that following the inspection by FDA/DSI, [redacted] notified CAP and provided them with [redacted] response to the 483 observations made during the inspection. [redacted] included the statement that the 0.1 N HCL certified reference was used as a quality control sample to assess the titration across the measured pH range to the end point of pH 7.0. The report also included the repeatability of the pH measurement by the inclusion of calibrators consisting of standard reference buffer solutions at pH 4.0 and 7.0 buffers. The response by CAP to [redacted] on April 20th, 2007 (copy is attached in the Appendix) stated the following:

"The College of American Pathologists' (CAP) laboratory Accreditation Program has completed its review of the material we requested concerning the FDA inspection that

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occurred on November 28-30, 2006 at your Laboratory. Based on this review, we find your laboratory continues to be in compliance with the CAP Standards for Laboratory Accreditation”.

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Reviewer's Comments: Please note that DSI already reviewed [redacted] response to the 483 observations and concluded that the response did not contradict the observations.

2. In addition, the applicant stated that because of the concern raised by the FDA inspector, they decided to assess whether running an additional reference control at the end of each analytical run would have had an impact on study data. They evaluated assay control and calibration values over the time period during which the study samples were tested (07/13/2005 – 11/19/2005). The mean of the 138 measurements of the 0.1 N HCL control over the entire course of the study was 1.035, with a standard deviation of 0.009 and Coefficient of Variation of 0.897%. Therefore, these data demonstrated that the assay was stable and reproducible for the one quality control check (i.e. 0.1 N HCL) over the time period during which the study samples were tested. Their conclusion was that their analysis indicated that there was no impact on study data by not including additional controls.

Reviewer's Comments: Although the additional analysis is supportive of the applicant's conclusions that the assay performance is unlikely to have changed from the beginning to the end of each run, the inclusion of additional controls would have provided a more definitive assessment.

The applicant also provided a certificate of accreditation as evidence that [redacted] is in general compliance with CLIA requirements (a copy is attached in the Appendix). The applicant stated that meeting CAP standards ensures that the lab has met CLIA standards. Per the Department of Health and Human Services, the CAP is recognized as an accrediting organization for clinical laboratories under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) program. The accreditation process of CAP provides reasonable assurance that the laboratories accredited by it meet the conditions required by Federal law and regulations. The applicant concluded that this information confirms that the assay method and operating procedures meet the CAP and CLIA standards.

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Reviewer's comments: This information was confirmed with the Centers for Medicare & Medicaid Services (CMS) (a copy of the e-mail is attached in the Appendix) because CMS is responsible for the administration of the CLIA program as shown on the certificate of accreditation.

Based on the totality of the supporting evidence discussed above the applicant has shown that the assay method and operating procedures used to measure the PD endpoint (MAO) met the CAP and CLIA standards required for clinical diagnostic laboratories.

Applicant's response to Question 1 (#2): an explicit list of all samples that were excluded (due to use of dry ice and mishandled samples) from statistical analysis.

The applicant provided an explicit list of all the samples that are excluded from the supplemental analyses of study 3001-B1-332-US as requested, with detailed explanations of who were

excluded from the modified intent to treat (mITT) and valid for efficacy (VFE) supplemental analyses due to gastric acid output arriving at either at ambient temperature or frozen, and due to the titration check sample results outside the specified acceptance limits of true concentration) or the potential error (dry ice box checked on Bill) in the shipping.

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Reviewer's Comments: From this reviewer's perspective, the applicant provided an explicit list of all the samples that were excluded from the statistical analysis in both the original NDA submission and the additional sensitivity analysis included in this submission. The list provided consisted of 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 inspection report (EIR).

FDA Response to Question 2:

From your reply, it is our understanding that in response to FDA concerns you have performed an additional sensitivity analysis for the primary endpoint, gastric acid output. Exclusion of the few suspected data, of which the procedure run had the titration check sample results outside the specified acceptance limits of true concentration), or where there were concerns on the handling of the samples, is acceptable. It is reassuring that the new analysis demonstrates results similar to those previously submitted in your application. The adequacy of the new analysis (Additional Supplemental Analysis of Maximum Acid Output Data) will be a matter for review. For your complete response, also submit the complete report for the new analysis (Additional Supplemental Analysis of Maximum Acid Output Data) including the data set.

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Applicant's Response to Question #2:

A complete report containing the results of the additional sensitivity analysis for the primary endpoint, gastric acid output was provided in the submission. Two (2) supplemental analyses of the primary endpoint (MAO) were performed by excluding the data from suspect samples described (subjects 000056 and 000060) for which the procedure run had the titration check sample results outside the specified acceptance limits of true concentration) and the one questionable sample (subject 000114) due to potential error in shipping handling (using dry ice). Summary statistics for the maximum acid output (MAO) previously submitted in the original NDA with that obtained from the additional analysis included in this submission are inserted in the tables below for comparison purposes:

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Appears This Way
On Original

**Table 2-2: Summary Statistics for Maximum Acid Output (mEq/h),
Modified Intent-to-Treat Population: Original Analysis**

Sequence	Statistics	Period 1 (Days 6-8)	Period 2 (Days 6-8)
Sequence I		Spheroid 40 mg	Tablet 40 mg
	N	28	28
	Mean ± SD	7.16 ± 5.07	7.54 ± 4.80
	Median	6.77	7.00
	Min, Max	0.56, 21.42	0.58, 18.96
Sequence II		Tablet 40 mg	Spheroid 40 mg
	N	24	24
	Mean ± SD	7.01 ± 4.82	7.04 ± 4.99
	Median	5.35	6.47
	Min, Max	1.68, 18.81	0.70, 23.62

Abbreviations: SD=standard deviation; Min=minimum; Max=maximum.

**Table 4-2: Summary Statistics for MAO (mEq/h)
Modified Intent-to-Treat Population: Supplemental Analysis 1**

Sequence	Statistics	Period 1 (Days 6-8)	Period 2 (Days 6-8)
Sequence I		Spheroid 40 mg	Tablet 40 mg
	N	27	27
	Mean ± SD	7.41 ± 4.99	7.80 ± 4.68
	Median	6.80	7.11
	Min, Max	0.62, 21.42	1.00, 18.96
Sequence II		Tablet 40 mg	Spheroid 40 mg
	N	23	23
	Mean ± SD	7.16 ± 4.86	7.15 ± 5.07
	Median	5.52	6.64
	Min, Max	1.68, 18.81	0.70, 23.62

Two (2) additional subjects (000056, 000060) were excluded due to \Leftarrow \Rightarrow 'titration check'

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**Table 4-5: Summary Statistics for MAO (mEq/h)
Modified Intent-to-Treat Population: Supplemental Analysis 2**

Sequence	Statistics	Period 1 (Days 6-8)	Period 2 (Days 6-8)
Sequence I		Spheroid 40 mg	Tablet 40 mg
	N	27	27
	Mean ± SD	7.41 ± 4.99	7.80 ± 4.68
	Median	6.80	7.11
	Min, Max	0.62, 21.42	1.00, 18.96
Sequence II		Tablet 40 mg	Spheroid 40 mg
	N	22	22
	Mean ± SD	7.02 ± 4.93	7.19 ± 5.19
	Median	5.35	6.68
	Min, Max	1.68, 18.81	0.70, 23.62

Two (2) additional subjects (000056, 000060) were excluded due to \Leftarrow \Rightarrow 'titration check' results outside the specified acceptance limits.

Subject 000114 was also excluded due to questionable sample mishandling status for period 2.

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These analyses indicated that the additional analysis results are similar to the original analyses for study 3001-B1-332-US, and support the same conclusion that the proposed delayed-release enteric-coated granule formulation and the delayed-release enteric-coated tablet formulation are pharmacodynamically comparable in the ability to suppress MAO in subjects with GERD and a history of EE.

Reviewer's Comments: The statistical analysis for the additional analysis was also similar to that obtained in the original analysis. However, these results are not presented here because the statistical approach is not acceptable.

FDA Response to Question 3:

We concur that a 'complete response' to the NDA Approvable Letter may consist of the supporting information provided in this background package in addition to our requests in our responses to Questions 1 and 2.

Reviewer's Comments: The complete response submitted by the applicant consisted of the supporting information provided in the background package (submitted on May 15th, 2007) and responses to the FDA request in the responses to Questions 1 and 2 which have already been discussed above.

3 Labeling Recommendations:

Applicant's proposed draft-labeling-text (showing key clinical pharmacology changes as "double underline" only) is inserted below:

CLINICAL PHARMACOLOGY

Pharmacokinetics

PROTONIX Delayed-Release Tablets are prepared as an enteric-coated tablets so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism**) with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (C_{max}) is 2.5 µg/mL, the time to reach the peak concentration (t_{max}) is 2.5 h and the total area under the plasma concentration versus time curve (AUC) is 4.8 µg·hr/mL. When pantoprazole is given with food, its t_{max} is highly variable and may increase significantly. Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6-14.0 L/h and its apparent volume of distribution is 11.0-23.6 L.

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4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Reviewer's Comments:

An information request asking the applicant to provide the listing of the specific volume of apple juice administered to the patients with and without the nasogastric tube was sent on 10/19/2007. Wyeth responded on 10/26/2007 with the following statement (see Appendix for more details):

Review of the source documents at the site has confirmed that there was no data listing of the specific volume of apple juice used for each administration in study 116 as expected for this study where documentation of a specific volume of apple juice would be made only when a deviation from the procedure of the protocol occurred. However, the site has confirmed that oral administration of pantoprazole granules was performed with strict adherence to the specifications outlined in the protocol

Therefore the volume of apple juice to be included in the label for administration with apple juice and with apple juice followed by administration via the NG tube was changed to the per protocol volume by the applicant as follows:

For administration with apple juice it was previously C □ that was stated in the label. This was changed to 5 mL as per the protocol. For administration through the NG tube, it was — C □ apple juice that was previously stated in the label. This was changed to 10 mL as per the protocol.

4 Appendix

4.1 Pharmacometrics Consult: None required since there was no PK/PD or POPPK data submitted.

4.3 Proposed Package Insert:

PROTONIX®
(pantoprazole sodium)
Delayed-Release Tablets

Delayed-Release C □

18 Page(s) Withheld

 Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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4.4 Correspondences and Data supporting the additional analysis:

- 1. └ └Response to FDA 483 (without attachments)

b(4)

5 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Complete List of the Samples that were excluded from the supplemental analysis:
Analyses

Site PI	Subject #	Deviation/Violation	Explanation	
T	000026	Early Term /sponsor request	Treatment period 1 gastric acid received frozen	
	000027	Early Term /sponsor request	Treatment period 1 gastric acid received frozen	
	000028	Early Term /sponsor request	Treatment period 1 gastric acid received frozen	
	000029	Early Term /sponsor request	Treatment period 1 gastric acid received frozen	
	000030	Early Term /sponsor request	Treatment period 1 gastric acid received frozen	
	000031	Early Term /sponsor request	Treatment period 1 gastric acid received frozen	
	000146	Early Term /sponsor request	Treatment period 1 gastric acid received frozen	
	000148	Early Term /sponsor request	Treatment period 1 gastric acid received frozen	
	000149	Early Term /sponsor request	Treatment period 1 gastric acid received frozen	
	000017		Gastric acid received at ambient temperature, both periods	Allowed to continue, patient not evaluable
			Gastric acid received at ambient temperature, both periods	Allowed to continue, patient not evaluable
J	000018	EIR: Improbable pH values for the 0-15 minute BAO sample with the pH of the initial aliquot		

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Site PI	Subject #	Deviation/Violation	Explanation
		listed as 1.8 and the pH of the diluted aliquot listed as 3.788. []	
[]	000021	Gastric acid received at ambient temperature, both periods	Allowed to continue, patient not evaluable
[]	000022	Gastric acid received at ambient temperature, both periods	Allowed to continue, patient not evaluable
[]	000024	Gastric acid received at ambient temperature, both periods	Allowed to continue, patient not evaluable
		Gastric acid received at ambient temperature, []	Allowed to continue, patient not evaluable
[]	000063	EIR: "Titration Check" results were outside the specified acceptance limits [] of true concentration), [] Gastric acid received at ambient temperature, []	Allowed to continue, patient not evaluable
		EIR: Impossible value listed for the diluted pH of the 31-45 minute BAO sample, as it shows the initial pH as 2.900 and the diluted pH as 6.548. []	
[]	000049	EIR: "Titration Check" results were outside the specified acceptance limits [] of true concentration), [] Gastric acid received at ambient temperature, []	Allowed to continue, patient not evaluable
[]	000051	EIR: "Titration Check" results were outside the specified acceptance limits [] of true concentration), []	Excluded from supplemental analyses 1 and 2 for mITT and VFE populations
[]	000056	EIR: "Titration Check" results were outside the specified acceptance limits [] of true concentration), []	Excluded from supplemental analyses 1 and 2 for mITT and VFE populations
[]	000060	EIR: "Titration Check" results were outside the specified acceptance limits [] of true concentration), []	
Site PI	Subject #	Deviation/Violation	Explanation
[]	000114	EIR: Dry ice box checked on bill, []	Excluded from supplemental analysis 2 for mITT and VFE populations

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Reviewer's Comments: All subjects in Table 6.3 except for the last 3 subjects (000056, 000060 and 000114) were already excluded from the mITT and VFE analysis populations in the original submission.

Synopsis of the Addendum to Study 3001B1-332-US (NDA 201-02845): Supplemental Analysis of Maximum Acid Output Data

This addendum was to provide a detailed description of the 2 supplemental analyses of the primary endpoint, maximum acid output (MAO), and the findings from these analyses for study 3001B1-332-US. These analyses were performed to address deficiencies raised by the FDA's Division of Gastroenterology Products in 15 March 2007 approvable letter and to provide additional information as a result of the written responses received to the Type A meeting request/background information package in the 23 July 2007 Fax.

The results from the original analyses of study 3001B1-332-US indicated that the pantoprazole granule formulation and the tablet formulation are pharmacodynamically comparable in the ability to suppress MAO in subjects with GERD for all 3 analysis populations (modified intent to-treat; mITT, Valid-for-Efficacy; VFE, and ITT).

Reviewer's Comments: Only the statistical methods are described below. The summary statistics results are included in the QBR.

Statistical Methods:

The statistical method used for the supplemental analyses of the primary endpoint (MAO) is the same as that used in the original analysis. The primary efficacy statistical analysis consisted of a comparison of the primary endpoint (MAO) between the marketed tablet (reference formulation) and the granule formulation (test formulation) in the mITT population. MAO was the average of the four 15-minute collections (mEq/h). If one 15-minute collection was missing, then the average of the remaining collections was used for the MAO value. If more than one 15-minute collection was missing, the MAO value was set to missing.

The primary endpoint was analyzed for all 3 populations (eg, mITT, VFE, and ITT). Pharmacodynamic (PD) comparability was determined for MAO using the approach (1-sided t-test or signed rank test, as appropriate).

Reviewer's Comments: As stated in my review in the original NDA, this statistical analysis approach using the one-sided t-test or signed rank test to establish pharmacodynamic comparability is not an acceptable approach. To establish comparability, the applicant should have used a 2-one-sided t-test approach. Tables summarizing the statistical analysis in the original analysis and the additional analysis are inserted below for informational purposes only although they suggest similarity in the conclusions obtained in the original analysis and the additional analysis excluding the 3 additional patients.

**Table 2-1: Statistical Analysis for Maximum Acid Output (mEq/h)
(Spheroid 40 mg - 1.2 x Tablet 40 mg): Original Analysis**

Analysis Population	N	Mean	SD	Median	t-Test	p-Value	
						Wilcoxon Signed-Rank Test	Test for Normality
ITT	71	-2.73	4.73	-2.21	0.000	0.000	0.283
mITT	52	-1.65	4.61	-1.34	0.006	0.002	0.104
VFE	51	-1.57	4.62	-1.33	0.010	0.003	0.091

Abbreviations: SD=standard deviation; ITT=intent-to-treat; mITT=modified intent-to-treat; VFE=valid-for-efficacy.

**Table 4-1: Statistical Analysis for MAO (mEq/h)
(Spheroid 40 mg - 1.2 * Tablet 40 mg):
Supplemental Analysis 1**

Analysis Population	N	Mean	SD	Median	T-Test	P-Value	
						Wilcoxon Signed-Rank Test	Test for Normality
ITT	71	-2.73	4.73	-2.21	0.000	0.000	0.283
MITT	50	-1.72	4.69	-1.36	0.006	0.002	0.146
VFE	49	-1.64	4.70	-1.35	0.009	0.003	0.134

Two (2) additional subjects (000056, 000060) were excluded for the MITT and VFE analyses due to 'titration check' results outside the specified acceptance limits.

**Table 4-4: Statistical Analysis for MAO (mEq/h)
(Spheroid 40 mg - 1.2 * Tablet 40 mg): Supplemental Analysis 2**

Analysis Population	N	Mean	SD	Median	T-Test	P-Value	
						Wilcoxon Signed-Rank Test	Test for Normality
ITT	71	-2.73	4.73	-2.21	0.000	0.000	0.283
MITT	49	-1.63	4.69	-1.35	0.009	0.003	0.128
VFE	48	-1.54	4.70	-1.34	0.014	0.005	0.109

Two additional subjects (000056, 000060) were excluded for the MITT and VFE analyses due to 'titration check' results outside the specified acceptance limits. Subject 000114 was also excluded due to questionable sample mishandling status for period 2.

Additional Information for Labeling by the different modes proposed (with applesauce, mixed with apple juice and mixed with apple juice and through the NG tube):

Wyeth's Response to CP IR (dated October 19th, 2007)

Reference is made to the Information Request for NDA 22-020 Protonix Delayed-Release Biopharm Information. b(4)

FDA's Question

The following request was received by fax from the FDA on 19 Oct 2007.

For NDA 22-020: Please provide the following information ASAP

Please provide a data listing of the volume of apple juice that was actually mixed with the Protonix Delayed-Release and administered to each subject for the "oral administration in apple juice" and the "nasogastric tube administration" in study 3001B1-116 US 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". b(4)

Wyeth's Response:

Study 3001B1-116 US was conducted at the Wyeth Research Clinical Pharmacology Unit, 1300 Wolf Street, Philadelphia, PA 19148 by Twenty-five (25) subjects were enrolled. This research site for the conduct of Wyeth clinical pharmacology studies is staffed by both b(4)

investigators and nursing staff specially trained in compliance necessary to assure the accurate collection of data for phase 1 studies. Review of the source documents at the site has confirmed that there was no data listing of the specific volume of apple juice used for each administration in study 116 as expected for this study where documentation of a specific volume of apple juice would be made only when a deviation from the procedure of the protocol occurred.

However, the site has confirmed that oral administration of pantoprazole granules was performed with strict adherence to the specifications outlined in the protocol as presented in Attachment 7 of the NDA:

The text below is present in the draft physician's prescribing information that was submitted in Wyeth NDA 22-020, Protonix Delayed Release b(4)

- Information for Patients, pages 10-11
- Dosage and Administration, pages 18-19

New revisions and a correction are incorporated in revised Information for Patients and Administration Options section of the draft USPI. This section is provided here for review and is written to be consistent with the instructions and method of administration used in study 3001-B1-116 US. A full revised draft label with marked changes will be submitted as soon as possible in follow up to this urgent response.

Information for Patients

Patients should be cautioned that PROTONIX[®] Delayed-Release Tablets SHOULD NOT BE SPLIT, CRUSHED, OR CHEWED. b(4)
PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of PROTONIX[®] Delayed-Release Tablets.

Patients should be cautioned that PROTONIX[®] SHOULD NOT BE CRUSHED OR CHEWED. PROTONIX b(4)
should be taken approximately hour before a meal.

Administration Options

PROTONIX - Oral Administration in Applesauce:

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

PROTONIX - Oral Administration in Apple Juice:

- Open
 - Empty intact granules into a small cup containing 5 mL of apple juice.
 - 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.
- b(4)

PROTONIX Nasogastric Tube Administration

For patients who have a nasogastric tube in place, PROTONIX 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 syringe 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 this step with at least 2 additional 10 mL aliquots of apple juice. No granules should remain in the syringe.

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/s/

Abi Adebawale
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Sue Chih Lee
11/7/2007 06:26:09 PM
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Clinical Pharmacology Review

NDA Number	22-020
Letter Date(s)	May 12 th , 2006 and February 28 th , 2007
Brand Name (Proposed)	Protonix [®]
Generic Name	Pantoprazole Sodium
Reviewer	Abimbola Adebawale Ph.D.
Acting Team Leader	Tapash Ghosh Ph.D.
OCPB Division	Division of Clinical Pharmacology 3 (DCP3)
OND Division	HFD-180
Applicant	Wyeth Pharmaceuticals, Philadelphia, PA
Related IND(s)	68,011
Submission Type; Code	505 (b) (2); 5S
Formulation,; Strength (s)	Delayed-Release Granules (40 mg)
Pharmacological Class	Proton Pump Inhibitor
Indication	Short-term treatment of gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE), maintenance of healing of EE, and long-term treatment of pathological hypersecretory conditions in adults \geq 18 years old.
Reference Listed Drug (RLD)	Protonix [®] Delayed-Release 40 mg Tablets

Table of Contents

1	Executive Summary	1
1.1	Recommendation	2
1.2	Phase IV Commitment	2
1.3	Summary of CPB Findings.....	2
2	QBR.....	4
3	Labeling Recommendations.....	13
4	Appendix	13

1 Executive Summary

This is a 505(b) (2) application for Protonix[®] (pantoprazole sodium) delayed-release oral formulation (equivalent to 40 mg pantoprazole). It is being proposed as an alternative to the approved tablet in adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE) who are unable to swallow the currently marketed tablet.

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1.1 Recommendation (s): From a clinical pharmacology perspective, this application is not acceptable because the pharmacodynamic comparability data of the pantoprazole sodium delayed-release granules and the currently marketed tablet cannot be used to support this NDA. This is because the documentation of the analytical method validation for the primary endpoint, maximal acid output (MAO) was inadequate and thus the results are not reliable. In addition, the results of an audit by the FDA Division of Scientific Investigations (DSI) of the facility that conducted the pharmacodynamic (PD) comparability study (# 3001B1-332-US), that found that the analytical data was "not acceptable for review" due to insufficient method validation, calibration, quality control and documentation. The statistical analysis using the one-sided t-test or signed rank test to establish therapeutic comparability was not an acceptable approach. The applicant did not submit data demonstrating bioequivalence between the to-be-marketed pantoprazole delayed-release granules and the currently marketed tablets either. Therefore, the comparative bioavailability of the pantoprazole delayed-release granules to the currently marketed tablets could not be established.

Comments to be conveyed to the Applicant for Future Considerations:

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. In addition, administration of the granules delivered via nasogastric (NG) tube was not bioequivalent to administration of the granules in applesauce when the 3 subjects were included in the analysis. Therefore the data indicates that administration of the granules via the NG tube is not an appropriate delivery method for the granules.

1.2 Phase IV Commitments: None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics (CPB) Findings:

The key element of the clinical development program supporting this NDA is the pharmacodynamic comparability study designed to bridge the proposed granule formulation to the marketed tablet formulation. Therefore, no efficacy trials were conducted with the pantoprazole sodium delayed-release granules. The applicant did not conduct a bioequivalence study between the to-be-marketed granule formulation and the marketed tablet formulation either.

The clinical development program consisted of 5 studies. The 2 pivotal clinical studies (3001B1-332-US and 3001B1-116-US) were conducted using the to-be-marketed pantoprazole sodium delayed-release granules formulation. Study 3001B1-332-US was performed to demonstrate the pharmacodynamic comparability of the to-be-marketed granules formulation to the marketed tablet formulation. Study 3001B1-116-US was carried out to establish bioequivalence among the 3 proposed methods for administration of the granules.

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Study # 3001B1-332-US was a multiple-dose, randomized, open-label, 2-period, crossover pharmacodynamic study. This reviewer will focus only on the pharmacodynamic assessment of pentagastrin stimulated maximal acid output (MAO). Dr. Nancy Snow (the reviewing medical officer) review dated 2/12/2007 addressed all other aspects of this study. This study was performed to demonstrate the pharmacodynamic comparability of a daily dose of 40mg granules formulation to the 40mg delayed-release tablets in subjects (N=76) with GERD and a history of EE following 1 week of administration. The primary pharmacodynamic measurement was the MAO measured from the 23rd to the 24th hour after the 7th day of administration of either the granule or tablet formulation.

The integrity of this PD comparability data cannot be established due to the inadequacy of the analytical method validation submitted which was also confirmed during a DSI audit of the facility where the study was conducted. In addition, although the overall mean \pm SD for MAO from all subjects (7.11 ± 4.98 mEq/h and 7.29 ± 4.77 mEq/h) for the granule formulation and the tablet formulation, respectively) was somewhat similar, the statistical analysis using the one-sided t-test or signed rank test to establish therapeutic comparability was not an acceptable approach. The hypothesis testing as proposed is one-sided and not a comparability test (i.e. 2 one-sided t-test approach). The unacceptability of this approach was previously conveyed to the applicant during a teleconference held with the FDA on June 23rd, 2005 and it was again conveyed to the applicant on July 20th, 2005. The applicant did not provide a rationale as to why they chose to continue with the one-sided test.

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 C_{max} , AUC_T , and AUC_{inf} , 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 C_{max} , AUC_T , and AUC_{inf} , 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 C_{max} , AUC_T , and AUC_{inf} , of the granules delivered via nasogastric (NG) tube in apple juice to granules in applesauce being within the BE limits of 80-125 %.

- 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.

Abimbola Adebawale, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 3

Tapash Ghosh, Ph.D.
Acting Team Leader
Division of Clinical Pharmacology 3

2. QBR

2.1 General Attributes

Mechanism of Action, Therapeutic Indications and Dosing Regimen:

Pantoprazole, sodium is a potent proton pump inhibitor (PPI) that inhibits the final pathway of secretion, the H⁺/K⁺-ATPase (the "proton pump") of gastric parietal cells. It is currently marketed as Protonix[®] in both a delayed-release tablet dosage form and as an I.V. formulation. The delayed release tablets were approved for the following indications in adults: short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis (EE) (approved on 02 February, 2000), maintenance of healing of EE and control of daytime and nighttime heartburn symptoms in subjects with gastroesophageal reflux disease (GERD) (approved on 12th June, 2001), pathological hypersecretory conditions including Zollinger-Ellison syndrome (approved on 19th April, 2002). The delayed-release granules are intended to be used for the same indications as the approved delayed-release tablets. The proposed treatment regimen is as follows:

Treatment of Erosive Esophagitis: The recommended adult oral dose is 40 mg given once daily for up to 8 weeks. For those patients who have not healed after 8 weeks of treatment, an additional 8-week course may be considered

Maintenance of Healing of Erosive Esophagitis: The recommended adult oral dose is P 40 mg, taken daily

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome (ZES): The dosage in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult starting dose is 40 mg twice daily. Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240mg daily have been administered. Some patients have been treated continuously for more than 2 years.

Regulatory Background of this NDA:

The current application (NDA 22-020) for the pantoprazole sodium delayed-release granule oral formulation (equivalent to 40 mg pantoprazole) is intended to be an alternative to the marketed delayed-release tablet formulation for patients who are unable to swallow the tablet (e.g. patients with esophageal structural anomalies and geriatric patients). The applicant has proposed the following three methods for administering the granules: a) oral administration in apple sauce b) oral administration in apple juice and c) administration through a nasogastric tube.

The key element of the clinical development program supporting this current NDA is the pharmacodynamic comparability study designed to bridge the proposed delayed-release granules formulation to the marketed tablet formulation. A similar pharmacodynamic (PD) bridging approach utilizing the endpoint of pentagastrin-stimulated MAO has previously been used to link the intravenous and oral routes of pantoprazole administration [Protocol 3001K1-309-US (GMR-32141)], to support the 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, (22nd March, 2001). A On June 18th, 2004, the applicant submitted a background package (submitted to IND 68,011 SN0017) for a meeting with the FDA that was to take place on 21 July 2004. In the background package Wyeth asked if the Agency agreed with a proposed PD equivalence approach to demonstrate the equivalence between the commercial pantoprazole sodium granules and the marketed delayed-release tablet. On 12 July 2004, FDA faxed their responses to questions in the background package. The response to the question with regards to the proposed PD equivalence approach was as follows:

“Yes. When the application is submitted, please also submit relevant PK study reports”.

Therefore the Agency did give a positive response to the PD equivalence approach provided that the relevant PK study reports were also submitted.

2.2 General Clinical Pharmacology

Q. What were the design features of the clinical pharmacology and/or pivotal clinical studies used to support efficacy and safety?

The design of the two pivotal clinical studies conducted was as follows:

Table 1: Pivotal Clinical Pharmacology Studies

Study Number	Study Description	Number of Subjects
3001B1-332-US	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).	76
3001B1-116-US	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.	25

Q. What was the basis of the pharmacodynamic endpoint(s)?

The basis of using pantoprazole in the treatment of GERD and associated symptoms is the ability of this PPI to inhibit gastric acid secretion. The pharmacodynamic endpoint used in the PD comparability study was based on the amount of gastric acid secretion determined. Gastric acid secretion can be assessed by pH measurements (stomach, esophagus) or measurement of acid output. Of these two measurements, gastric acid output (GAO) is considered to be more precise than the pH measurement. This is because gastric acid output (GAO) is the product of volume and hydrogen acid ion concentration (assessed by titration to pH 7.0). This measurement is believed to more accurately reflect the amount of gastric acid secreted than simple pH measurements, which do not account for differences in the volume secreted. In addition, the pH measurement may vary depending upon the position of the pH probe.

The suppression of pentagastrin-stimulated maximum acid output (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 endpoint in the PD comparability study. The applicant stated that this endpoint was chosen to demonstrate pharmacodynamic (PD) comparability because inhibition at the end of the dosage interval, once at steady state, can assure gastric acid control during the entire 24-hour period.

Q. Are pantoprazole sodium delayed-release granules pharmacodynamically comparable to the approved tablets?

No the granules are not pharmacodynamically comparable to the tablets. In study # 3001-B1-332-US, although the overall mean \pm SD for MAO from all subjects (7.11 ± 4.98 mEq/h and 7.29 ± 4.77 mEq/h) for the granule formulation and the tablet formulation, respectively) was somewhat similar, the statistical analysis using the one-sided t-test or signed rank test to establish therapeutic comparability was not an acceptable approach. In addition, the integrity of the pharmacodynamic comparability study (# 3001-B1-332-US) could not be established because of insufficient method validation, calibration, quality control and documentation identified by a DSI audit.

Study # 3001-B1-332-US was a multiple-dose, randomized, open-label, 2-period, crossover pharmacodynamic comparability study in subjects (n=76) with GERD and a history of Erosive Esophagitis (EE). This study compared a 40-mg dose of the pantoprazole sodium delayed-release granules administered on a teaspoon of applesauce and the currently marketed pantoprazole sodium delayed-release 40-mg tablet. The subjects were instructed to take study medication half-hour before breakfast. The primary pharmacodynamic endpoint was the suppression of pentagastrin stimulated maximal acid output (MAO) at steady state (from hour 23 to 24) following administration of a 40 mg dose of each formulation once daily for 1 week. There was a washout period between each treatment period of 14 to 21 days. The primary population analyzed in this study was the modified intent-to-treat (mITT) population. The mITT population included all randomly assigned subjects who took at least 1 dose of test article in each of the treatment periods and had pentagastrin-stimulated MAO data after the last dose of test article for both treatment periods.

The results of this study as shown in the table below suggest that the mean MAO for the granule and tablet pantoprazole sodium formulations were numerically similar in their ability to suppress MAO in subjects with GERD.

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

However, the statistical analysis using the one-sided t-test or signed rank test to establish therapeutic comparability was not an acceptable approach. The hypothesis testing used was a one-sided test and not a comparability test (i.e. 2 one-sided test approach). This was confirmed with the statistical reviewer Dr. W. Chen. The unacceptability of this approach was previously conveyed to the applicant during a teleconference held with the FDA on June 23rd, 2005 and it was again conveyed to the applicant on July 20th, 2005. Specifically, the FDA stated the following:

FDA Response:

3. **As conveyed to you during the June 23, 2005 teleconference: If it is not possible to establish pharmacodynamic equivalence due to technical limitations of the pharmacodynamic analysis, then establishing therapeutic comparability using a one-sided t-test or signed rank test is not an acceptable approach.**

Reviewer's Comments: The applicant did not provide a rationale as to why they decided to still use the one-sided test.

2.5 General Biopharmaceutics:

Drug Product Composition:

Table 3: Composition of Pantoprazole Sodium Delayed-Release Granules

Component	Quantity
Pantoprazole Sodium Sesquihydrate	45.11 ^a
Microcrystalline Cellulose	

b(4)

This concept is supported by the PK data that was reported in a pilot bioequivalence study performed with a prototype granule formulation [Protocol 3001A1-114-US (53163)] compared to the delayed-release tablets. There was similar AUC but a lower C_{max} with the granule formulation compared to that of the delayed-release tablet. The lower C_{max} with the granules was anticipated, based on the way each formulation travels through the gastrointestinal tract. It is conceivable that granules can be dispersed rapidly and relatively evenly along the gastrointestinal tract in a manner less dependent of gastric emptying than the intact tablet. As a result, the drug release/absorption phase for the granules is longer, resulting in a flatter plasma concentration-time curve (lower C_{max}), as compared to the tablet. For AUC, the 90% confidence interval (CI) for the ratios of the geometric means of the granules sprinkled on applesauce to the tablet was 84.7% to 95.9% and for the pantoprazole sodium granule suspension to the tablet was 88.1% to 99.8%; both of these sets of confidence intervals were within the bioequivalence limits of 80% to 125%. For C_{max} , the 90% CI was 55.6% to 70.0% for the ratio of granules sprinkled on applesauce to tablet and was 58.9% to 74.1% for the ratio of granule suspension to tablet. The pantoprazole sodium delayed-release granules did not meet the criteria for bioequivalence limits for C_{max} .

b(4)

Furthermore, given that pharmacodynamic comparability has been established between the IV and oral tablet administration, it is also conceivable that the somewhat different pattern of absorption may not affect the ability of the delayed-release granule formulation to suppress acid secretion over the prescribed dosing interval as compared to the delayed-release tablet formulation.

Reviewer's Comment: The statement by the applicant above indicates that the results of the bioequivalence study conducted with their pilot formulation contributed to their decision to conduct a PD comparability study instead of a BE study. It should be noted that the data from the BE study could only be used to support development because there were some differences in the pilot formulation used and the to-be-marketed granule formulation (TBMF). The sponsor did not conduct any BE study to link the pilot formulation to the TBMF either. For the pilot granule formulation, (

) and to match the pantoprazole sodium delayed release tablet formulation. Additionally, (

) qualitatively match the enteric coat of the tablet. (Therefore, the BE data obtained with the pilot formulation could only be used to assist in the development of the granule formulation. However, the applicant should have considered conducting a BE study between the granule and tablet or their pilot formulation and the TBMF to provide a more robust clinical bridge (for safety and efficacy) data.

b(4)

Q. Were various dosing administration methods bioequivalent?

Study # 3001B1-116-US demonstrated that pantoprazole sodium delayed release granules administered with apple juice were found to be bioequivalent to the granules administered with applesauce. However, administration the granules delivered via NG tube in apple juice to granules in applesauce were not bioequivalent because of the data from 3 subjects who only received a small fraction of the dose due to trapping of the majority of the dose in the clogged

NG tube. Exclusion of these three subjects from the statistical analysis resulted in the bioequivalence of the granules administered via the NG in apple juice to granules administered with applesauce.

Study # 3001B1-116-US was an open-label, single-dose, randomized, 3-period crossover study in 25 healthy subjects. Each subject received a single 40 mg dose of pantoprazole sodium delayed-release granules under fasting conditions sprinkled over applesauce (Treatment A), mixed with apple juice (Treatment B) and administered through an NG tube (Treatment C). Each period was separated by a washout interval of at least one day. A summary of the PK parameters and the 90% CI are shown in the table below:

Regimen		C_{max} (ng/mL)	t_{lag} (h)	t_{max} (h)	AUC_T (h)	AUC (ng.h/mL)
Granules in applesauce	Mean ± SD ^a	1969 ± 670	0.50	2.0	3993± 1517	4029± 1521
Granules in apple juice	Mean ± SD	1863± 456	0.50	2.5	3841± 1420	3890± 1422
Granules in NG tube	Mean ± SD	1961 ± 897	1.0	2.0	3606± 1991	3638 ± 1998
Geometric Mean Ratio ^b		97.88	---	---	97.70	98.08
Geometric Mean Ratio ^c		88.24			77.42	77.72
90% CI ^b		85.07-112.62	---	---	84.90 – 112.42	85.33 – 112.72
90% CI ^c		67.84 – 114.77	---	---	58.66– 102.18	59.13 – 102.14

a: median values reported for t_{lag} and t_{max} . b: Ratio of granules in apple juice to applesauce. c: Ratio of granules in NG tube to applesauce

Table 5: Summary of Pharmacokinetic Parameters for Pantoprazole Granules (N = 22; 3 subjects excluded)

Regimen ^a	C_{max} (ng/mL)	t_{lag} (h)	t_{max} (h)	AUCT (ng.h/mL)	AUC (ng.h/mL)
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 ^b (GAJ)	101.97	---	---	100.05	100.42
Geometric mean ratio ^c	113.39			99.96	99.94
(GNG) 90% CI ^b (GAJ)	92.4 – 112.5	---	---	94.4 – 106.1	94.8 – 106.4
90% CI ^c (GNG)	102.7 – 125.2	---	---	94.3 – 106.0	94.3 – 105.9
a: Values are expressed as mean ± SD, except for tlag and tmax b for which medians are reported: Ratio of granules in apple juice to applesauce c: Ratio of granules in NG tube to applesauce;					

Reviewer's Comments: The data in the tables above demonstrates the following:

- For C_{max} , AUC_T , and AUC , the 90% CI's for the ratio of the geometric means of the granules in apple juice to granules sprinkled on applesauce are within the BE limits of 80-125%.
- The 90% CI's for the ratio of the geometric means for C_{max} , AUC_T , and AUC , of the granules delivered via nasogastric (NG) tube 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 C_{max} , AUC_T , and AUC , of the granules delivered via nasogastric (NG) tube to granules in applesauce being within the BE limits of 80-125%.
- However, the applicant noted that the C_{max} ratio of the geometric means of the pantoprazole sodium delayed release granules administered through an NG tube reached the upper bioequivalence limit of 125% (i.e. 125.2%). The applicant stated that this was probably because an NG tube administration produced relatively narrow distribution of the granules along the GI tract resulting in slightly higher C_{max} values compared with granules administered with applesauce or apple juice.
- Although exclusion of the 3 subjects resulted in bioequivalence, there could still be 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. Therefore, this delivery method of administration may not be appropriate.

2.6 Analytical

Q. *Were the analytical methods used for the determination of pantoprazole in gastric fluid adequately validated?*

No, the analytical method used for the determination of pantoprazole in gastric fluid was not adequately validated.

Method	The titration of the gastric secretion to a pH of 7.0 will measure Total Titrable Acidity, the amount of free HCL plus all other acids contained in the sample (including bound H ⁺ such as protein) by titrating gastric sample to PH 7.0 with 0.1N sodium hydroxide and recording the volume of NaOH titrated.
Matrix	Gastric Fluid
Accuracy (% Theoretical)	ND
Precision (% CV) <i>Within-Day</i> <i>Between-Day</i>	1 % 1.2 %
Standard curve range	No standard curve range. Only one titration check (1 mL 0.1N HCl diluted with 9 mL of water). This was however, not representative of the study samples
Sensitivity (LOQ)	ND
Selectivity	ND
Recovery	ND
Stability	ND
Conclusion	Method validation is not acceptable

ND=Not determined

Reviewer's Comments: In addition, an audit by the Division of Scientific Investigations (DSI) of the clinical and analytical portions of the pharmacodynamic comparability study (# 3001B1-332-US) found that the analytical data for the primary pharmacodynamic endpoint (MAO) was not acceptable for review. This was 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 drug product, the safety and efficacy of pantoprazole delayed release granules cannot be determined.

Q. Were the analytical methods used for the determination of pantoprazole in plasma adequately validated?

Yes, the analytical method used for the determination of pantoprazole in plasma was adequately validated.

Method	LC/MS/MS
Compound	Pantoprazole
Internal Standard	C 7
Matrix	Plasma
Accuracy (% Theoretical) <i>Within-Day</i> <i>Between-Day</i>	-13.65 % to 12.13 % -0.76% to 4.96 %
Precision (% CV) <i>Within-Day</i> <i>Between-Day</i>	2.16 % to 9.48 % 3.45 % to 11.81 %
Standard curve range	10-500 ng/mL ($r^2 \geq 0.994$)
Sensitivity (LOQ)	10 ng/mL

b(4)

Selectivity	No significant peaks at the retention times of pantoprazole and the IS were observed
Stability	Less than 10 % degradation was obtained following Freeze/Thaw (human plasma; -20 °C/37 °C) 4 cycles and Freeze/Thaw (human plasma; -20 °C/Room Temperature) 3 cycles Long-Term (plasma; -20 °C) 44 days resulted in less than 5 % degradation)
Conclusion	Method validation is acceptable

3 Labeling Recommendations:

b(4)

The applicant's key label recommendations and product characteristics for PROTONIX (pantoprazole sodium) Delayed-Release were as follows:

Clinical Pharmacology:

- PROTONIX applesauce or apple juice. are bioequivalent when administered orally in through a nasogastric tube

b(4)

Dosage and Administration:

b(4)

Reviewer's Comments: Labeling recommendations are deferred until after the applicant provides adequate data to support this NDA.

4 Appendix

4.1 Pharmacometrics Consult: None required since there was no PK/PD or POPPK data submitted.

4.2 DSI Consult:

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

DATE: December 22, 2006

TO: Mary H. Parks, M.D., Director
Division of Metabolism and Endocrinology Products
FROM: Michael F. Skelly, Ph.D., Pharmacologist
Division of Scientific Investigations (HFD-48)
THROUGH: C.T. Viswanathan, Ph.D., Associate Director – Bioequivalence
Division of Scientific Investigations (HFD-48)
SUBJECT: Review of EIRs Covering NDA 22-020, Protonix Delayed Release
(pantoprazole sodium), Sponsored by Wyeth Pharmaceutical Inc.

b(4)

At the request of DMEP, the Division of Scientific Investigations audited clinical and analytical portions of the following bioequivalence study. **Study# 3001B1-332-US: A Randomized, 2-Period, Crossover, Pharmacodynamic Comparability Study Comparing a Pantoprazole Sodium Spheroid Formulation to the Currently Marketed Tablet Formulation in Subjects with GERD and a History of Erosive Esophagitis.** Following the inspection at

FDA 483 was issued. Following the inspection at
no Form
Form FDA 483 was issued. The objectionable observations and our evaluation are provided below:

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.

Thus, the assay method for the pharmacodynamic endpoint measurement was not calibrated in each run, and there were insufficient quality control samples during the study either to demonstrate accuracy and precision or to justify run acceptance. The "titration check" sample and a single sample each of gastric aspirate for "basal acid output" and "maximal acid output" were not representative of the study samples, and do not suffice to validate the assay.

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

There were almost no details of how personnel actually did the validation and study testing.

b(4)

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 Personnel did not reject these runs, and re-assay the samples, as required by the established procedure.

b(4)

4. The analyst did not sign and date all original data entries on the day of acquisition. Example: One set of initials for work dated 8/25/05 and 8/26/05

In the example, the data entries on each day are not attributable to an individual analyst.

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. The page containing the crucial data was not printed. Only a handwritten entry documented the instrumental result. DSI reviewed (response to the observations; the response does not contradict the observations.

b(4)

Conclusions:

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. After you have reviewed this transmittal memo, please append it to the original NDA submission.

Michael F. Skelly, Ph.D.

Pharmacologist

Page 4 of 4 - NDA 22-020, Protonix Delayed Release ()

Sponsored by Wyeth Pharmaceutical Inc.

Final Classifications:

NAI - ()

()

VAI - ()

b(4)

Recommendation: Pharmacodynamic data from study 3001B1-332-US are not acceptable for review.

cc:

DMEP/Moreno/NDA 22-020/

HFA-224

HFD-45/RF

HFD-48/Himaya

HFD-48/CF

HFR-PA250/VanLeeuwen

HFD-SE1535/Frazier

OCP/DCP3/Adebowale

Drafted: MFS 12/22/06

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/s/

Michael Skelly

18 Page(s) Withheld

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Draft Labeling (b4)

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4.4 Individual Study Reviews:

Study # 13001B1-332-US, CSR-62845:

b(4)

Title: A randomized, 2-period, crossover, pharmacodynamic comparability study comparing a pantoprazole sodium spheroid (also referred to as granules) formulation to the currently marketed tablet formulation in subjects with GERD and a history of erosive esophagitis (EE)

Objective: The objective was to demonstrate pharmacodynamic comparability between the to-be-marketed pantoprazole sodium delayed-release spheroid formulation and the currently marketed pantoprazole sodium delayed release tablet.

Study Site: Multi-center (All in the US)

Analytical Study Site: ☐

Study Period: (DATE OF FIRST ENROLLMENT): 05 Jul 2005

(DATE OF LAST COMPLETION): 28 Nov 2005

Study Design: This was a multiple-dose, randomized, open-label, 2-period, 2-sequence crossover study. Each subject participated in the study for approximately 9 weeks, including up to a 3-week pre-study screening period, two 1-week treatment periods 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.

Study Population: Subjects (aged 18-65 years inclusive) with GERD and a history of EE documented by endoscopy within 5 years before the screening visit requiring continued PPI treatment with a negative *Helicobacter pylori* test (urease breath or CLO test) and serum gastrin ≥ 150 pg/mL.

Test product, dose and mode of administration, batch number: Pantoprazole sodium 40-mg delayed-release spheroids for oral administration, (batch # 2005B0001). It was administered each morning once daily ½ hour before breakfast for 7 consecutive days. The spheroid formulation was to be sprinkled on a teaspoonful of applesauce followed by water (~240 mLs). It should not be chewed and it should be taken within 2 hours of preparation.

Reference therapy, dose and mode of administration, batch number: Pantoprazole sodium 40-mg delayed release tablets for oral administration, (batch # 5001499268). It was administered each morning once daily ½ hour before breakfast for 7 consecutive days. The tablet formulation was to be taken with water (~240 mLs).

Each dose was to be preceded by an overnight fast of at least 8 hours. The first dose was administered at the study site under the direction of the investigator or designee. The seventh dose was also administered to the subject by the study staff. The subjects were instructed to return the study medication packages and any unused test article when they returned to the clinic on day 6 of each treatment period. Each subject was randomly assigned in a 1:1 ratio to one of 2 treatment sequences.

Other Dugs Permitted

Gelusil antacid tablets (Batch # 03434B and 14745B, Pfizer market Product) were dispensed during the screening period.

- Gelusil tablets were to be taken as needed for relief of heartburn, acid regurgitation, or related symptoms that lasted for 5 or more minutes, but not within 8 hours before any pH-metry evaluation or during the 24-hour pH measurements (i.e. after 8 PM on day 6) or GAO output measurements. The subjects were instructed not to resume use of Gelusil until after each GAO assessment was completed.
- Gelusil was to be taken between evaluations and during the washout period. The subjects were not to take more than 12 Gelusil tablets in a 24-hour period.
- The subjects were instructed to call the study doctor if any of the symptoms lasted for more than 3 days.

Pentagastrin: Pentagastrin (250 mcg/mL, batch # 1B, ☐

☐ ☐ was administered subcutaneously at a dose of 6.0 mcg/kg immediately after collection of the BAO samples. Screening laboratory evaluations included fasting serum gastrin. This test was performed when the subject first presented for screening. If the result of the fasting serum gastrin was ≤ 150 pg/mL, then the subject was eligible for enrollment. If the value was >150 pg/mL, the test was repeated after the subject had been off PPIs for at least 14 days and off H2RAs for at least 3 days.

Sample Size and Power

From a previous study (3001K1-309-US), the mean and the standard deviation for the derived variable (MAO_{spheroid} - 1.2*MAO_{tablet}) to be used for testing PD comparability is around – 1.45 and 2.68, respectively. The mean represents approximately 20% of MAO_{tablet}. Therefore, with a sample size of 45 evaluable subjects, the statistical power for detecting a 20% difference in MAO is expected to exceed 90% at the 0.05 significance level. Approximately 55 subjects will be randomized to ensure that at least 45 individuals have evaluable PD data for both treatment periods.

Pharmacodynamic assessment methods:

Procedure for Day 7

1. Record vital signs approximately 1 hour before administration of study medication.
2. Insert pH probe approximately 1 hour before administration of study medication and begin pH monitoring.
3. Administer study medication.
4. Serve breakfast approximately ½ hour after study drug administration.
5. Serve lunch approximately 5 hours after study drug administration.
6. Serve dinner approximately 10 hours after study drug administration.

Procedure for Day 8

1. Record vital signs.
2. Discontinue pH monitoring approximately 21 hours after administration of study medication and remove pH probe.
3. Insert NG tube during hour 21.
4. Immediately before the end of hour 22, evacuate gastric contents.
5. Collect all gastric secretions during hours 22 to 23 for determination of BAO.
6. At hour 23, administer pentagastrin.
7. Collect all gastric secretions during hours 23 to 24 for determination of MAO.
8. Remove the NG tube at the end of the gastric secretion collection period.

PD Sampling and Analytical Method: During the BAO and MAO collection periods, gastric secretions were continuously collected by intermittent suction so that all gastric juice was removed for the duration of the acid collection period. Aliquots of the secretions were collected every 15 minutes for 1 hour for both BAO and MAO. The gastric aspirate samples were analyzed for total acid content by titration to pH 7.0 by the central laboratory.

Pharmacodynamic End-Points

Primary: The suppression of 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

Secondary pharmacodynamic variables included the following:

- Basal acid output (BAO) at steady state.
- Integrated gastric acidity (AUC of the standardized hydrogen ion concentration versus time from 0 to 24 hours at steady state).
- Mean and median intragastric pH.
- Mean and median intraesophageal pH.

- Percentage of time that intragastric pH was >3 and pH was >4.
- Percentage of time that intraesophageal pH was <4.
- Number of reflux episodes.
- Number of reflux episodes longer than 5 minutes.
- Duration of the longest reflux episode.

Statistical Analyses: Pharmacodynamic parameters were analyzed for 3 populations: modified intent-to-treat (mITT), valid-for-efficacy (VFE), and intent-to-treat (ITT). The primary population for PD analysis was the modified intent-to-treat (mITT) population because MAO data in both periods were needed in order to perform the statistical comparisons. The mITT population included all randomly assigned subjects who took at least 1 dose of test article in each of the treatment periods and had pentagastrin-stimulated MAO data after the last dose of test article for both treatment periods. Some gastric acid specimens were handled improperly during the study. The MAO and BAO measurements from these specimens were considered invalid data (not qualified for mITT and valid-for-efficacy [VFE] analyses).

Baseline Comparisons:

Baseline comparisons were made for the safety, mITT, VFE, and ITT populations. Baseline demographic, disease characteristics, and other background medical history information were summarized to evaluate the comparability of treatment sequences. The Fisher exact test was used for variables reported as nominal attributes (e.g., sex, race, ethnic origin, and degree of EE), and analysis of variance (ANOVA) with sequence as a factor in the model was performed for continuous variables such as age, weight, height, and body mass index for the comparisons of baseline parameters between the 2 sequences.

Primary Efficacy Analyses:

The primary efficacy statistical analysis consisted of a comparison of the primary endpoint (MAO) between the marketed tablet (reference formulation) and the spheroid formulation (test formulation) in the mITT population. MAO was the average of the four 15-minute collections (mEq/h). If one 15-minute collection was missing, then the average of the remaining collections was used for the MAO value. If more than one 15-minute collection was missing, the MAO value was set to missing.

PD comparability was determined for MAO using the approach (1-sided t-test or signed rank test, as appropriate) used in study 3001K1-309-US, in which the comparability of the IV and tablet formulations was demonstrated (*Reviewer's Comment: this was reviewed by Dr. Hugo Gallo-Torres and found acceptable*). The comparison in the current study was based on the difference between the value following the last tablet dose and the value following the last spheroid formulation dose.

The null hypothesis tested was:

$$H_0: MAO_{\text{spheroid}} - MAO_{\text{tablet}} \geq 0.2 MAO_{\text{tablet}}$$

and the alternative hypothesis was:

$$H_1: MAO_{\text{spheroid}} - MAO_{\text{tablet}} < 0.2 MAO_{\text{tablet}}$$

Or equivalently,

$$H_0: MAO_{\text{spheroid}} - 1.2 MAO_{\text{tablet}} \geq 0 \text{ versus } H_1: MAO_{\text{spheroid}} - 1.2 MAO_{\text{tablet}} < 0.$$

The normality of the difference was tested at an alpha level of 0.05 using the Shapiro-Wilks test. If the assumption of normality was not rejected, the p-value from the 1-sided t-test was reported. Otherwise, the p-value from the nonparametric statistics (Wilcoxon signed-rank test) was reported.

If the null hypothesis was rejected at an alpha level of 0.05, it was concluded that the acid output for the spheroid formulation was at most 20% greater than that of the tablet formulation and therefore, the 2 formulations of pantoprazole were comparable. The descriptive summary statistics (eg, n, mean, standard deviation [SD], median, and range) was also provided for each period and treatment sequence. Additionally, the carryover and period effect was tested using the mixed model by using formulation, period, and sequence as fixed effects, and subject within sequence as random effect.

Reviewer's Comments: This statistical test is not acceptable. The applicant was told at previous meetings that (June 23rd and July 20th, 2005) that a one sided t-test would not be an acceptable approach for establishing therapeutic comparability).

Secondary Efficacy Analyses: The analysis for the secondary endpoint (BAO) was similar to that described above for the primary endpoint (MAO). The adjusted means, the mean difference, and its 2-sided 95% CI between formulations for the percentage of time that intragastric pH was >4 were obtained for the mITT pH population from the mixed model by using formulation, period, and sequence as fixed effects, and subject within sequence as random effect. Descriptive statistical summaries are presented for all other secondary endpoints.

Handling Dropouts or Missing Data

For the ITT population, if a subject had a missing MAO or BAO value for 1 of the periods, the mean value of the MAO or BAO from the same sequence and period was assigned (imputed). If a subject had data for only 1 period, but not for the other, the subject was excluded from the mITT and VFE population analysis. If a subject's gastric acid specimens were handled improperly, the MAO and BAO data from those specimens were excluded from the mITT population analysis.

Results:

Number of Patients per Site:

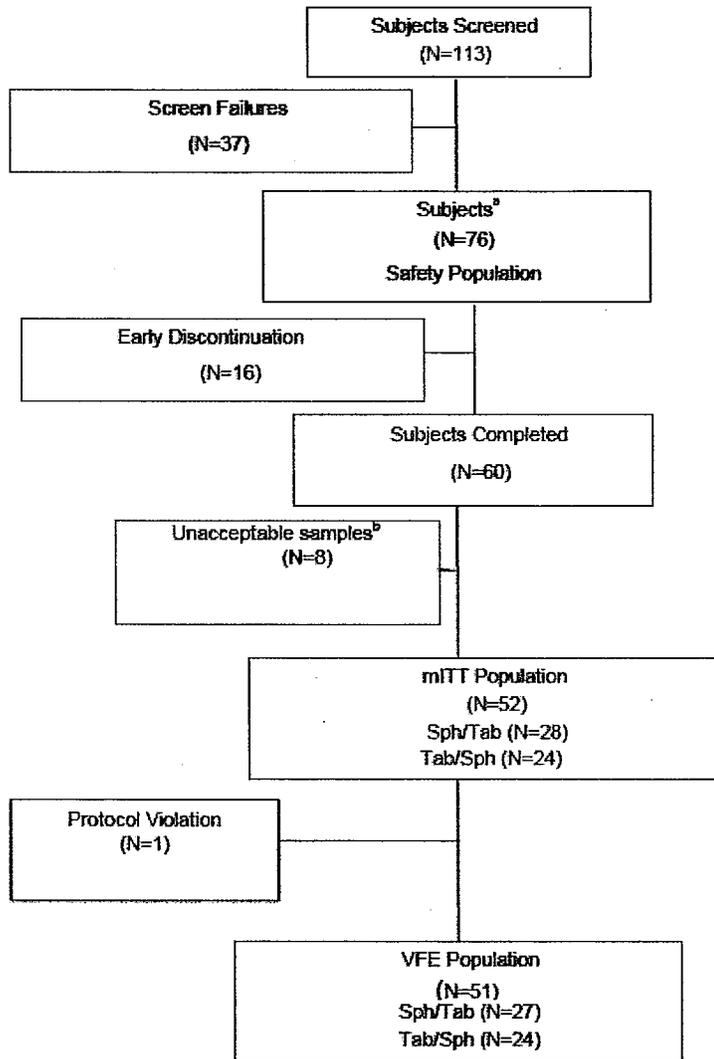
Subject Participation Status
Summary of Subjects by Investigator

Investigator	Completion Status	Population	Number of Subjects
[]	Completer	Safety	5
	Early Discontinuer	SFail	6
	Early Discontinuer	Safety	10
[]	Completer	Safety	10
	Early Discontinuer	SFail	5
[]	Completer	Safety	14
	Early Discontinuer	SFail	9
	Early Discontinuer	Safety	2
[]	Completer	Safety	11
	Early Discontinuer	SFail	6
	Early Discontinuer	Safety	1
[]	Completer	Safety	12
	Early Discontinuer	SFail	7
	Early Discontinuer	Safety	2
[]	Completer	Safety	8
	Early Discontinuer	SFail	2
	Early Discontinuer	Safety	1
[]	Early Discontinuer	SFail	2

b(4)

Patient Disposition:

Figure 8.1-1: Subject Disposition and Study Population



Abbreviations: mITT=modified intent-to-treat; Sph=spheroid; Tab=tablet; VFE=valid-for-efficacy; ITT=intent-to-treat.; a. A total of 71 patients comprised the ITT population (at least 1 dose of test article and had at least 1 MAO measurement); b. These subjects were excluded from the mITT population due to improperly handled gastric specimens (received at ambient temperature for 1 or both treatment periods).

Five (5) subjects in the safety population were excluded from the ITT population because they did not complete at least 1 MAO measurement. A total of 71 subjects who took at least 1 dose of test article and had at least 1 MAO measurement comprised the ITT population: 37 subjects (97%) in the spheroid/tablet treatment sequence and 34 subjects (90%) in the tablet/spheroid treatment sequence.

Eight (8) subjects in the safety population were excluded from the mITT population because of improperly handled gastric specimens (received at ambient temperature for 1 or both treatment periods). Sixteen (16) subjects in the safety population were excluded from the mITT population because they did not complete MAO measurement for both treatment periods. Therefore, 52 subjects who took at least 1 dose of test article in each of the treatment periods and had pentagastrin-stimulated MAO data after the last dose of test article for both treatment periods comprised the mITT population: 28 subjects (74%) in the spheroid/tablet treatment sequence and 24 subjects (63%) in the tablet/spheroid treatment sequence.

One (1) subject in the mITT population was excluded from the VFE population because the subject took a prohibited medication before the *H. pylori* test. A total of 51 subjects comprised the VFE population: 27 subjects (71%) in the spheroid/tablet treatment sequence and 24 subjects (63%) in the tablet/spheroid treatment sequence.

Demographic and Other Baseline Characteristics

The sponsor presented these data in a series of Tables, for the four populations studied (Safety, mITT, VFE and ITT). All subjects were younger than 65 y (mean age of 44 y, range=21-63y), 55% were male and 45 % were female, mostly white (75 %), with an average weight of 91.5 kg, height 170.9 cm, and mean body mass index of 31.3 kg/m². None of the subjects were known to have any illnesses at baseline (other than a previous history of GERD) that might interfere with the activity of the study medication or the interpretation of the results. Many subjects had a history of chronic, stable medical conditions that would not interfere with the conduct of the study. Demographic and baseline characteristics of the subjects in the mITT and VFE populations did not differ appreciably from those of the safety population. There were no statistically significant differences between treatment sequences in demographic or baseline characteristics in the safety or other populations (mITT, VFE, and ITT).

Table 9.2-1: Demographic and Baseline Characteristics, Modified Intent-to-Treat Population

Characteristic	p-Value	-----Treatment Sequence-----		Total (n=52)
		Spheroid 40 mg /Tablet 40 mg (n=28)	Tablet 40 mg /Spheroid 40 mg (n=24)	
Age (years)				
N		28	24	52
Mean	0.149 ^a	47.18	42.88	45.19
Standard Deviation		11.92	8.66	10.67
Minimum		21.00	29.00	21.00
Maximum		63.00	62.00	63.00
Median		48.50	42.00	44.00
Sex	1.000 ^b			
Female		12 (42.86)	11 (45.83)	23 (44.23)
Male		16 (57.14)	13 (54.17)	29 (55.77)
Race	0.310 ^b			
Asian		2 (7.14)		2 (3.85)
Black or African American		1 (3.57)		1 (1.92)
Native Hawaiian or Other Pacific Islander		1 (3.57)		1 (1.92)
Other		6 (21.43)	3 (12.50)	9 (17.31)
White	1.000 ^b	18 (64.29)	21 (87.50)	39 (75.00)

Hispanic or Latino		12 (42.86)	10 (41.67)	22 (42.31)
Non-Hispanic and Non-Latino		16 (57.14)	14 (58.33)	30 (57.69)
Baseline Height (cm)				
N		28	24	52
Mean	0.961 ^a	170.32	170.18	170.26
Standard Deviation		10.32	8.74	9.53
Minimum		151.13	152.40	151.13
Maximum		189.23	190.50	190.50
Median		171.45	170.18	170.18
Baseline Weight (kg)				
N		28	24	52
Mean	0.905 ^a	89.63	90.23	89.90
Standard Deviation		16.14	19.91	17.80
Minimum		56.70	60.70	56.70
Maximum		130.00	129.50	130.00
Median		89.51	87.65	88.60
Body Mass Index (kg/m ²)				
N		28	24	52
Mean	0.917 ^a	30.93	31.10	31.01
Standard Deviation		5.27	6.40	5.76
Minimum		23.17	22.97	22.97
Maximum		44.89	45.31	45.31
Median		29.92	30.18	30.13
Degree of Erosive Esophagitis				
	0.662 ^b			
Deep Ulceration		2 (7.14)		2 (3.85)
Superficial Ulceration 10% to 50%		7 (25.00)	6 (25.00)	13 (25.00)
Superficial Ulceration <10%		19 (67.86)	18 (75.00)	37 (71.15)

a. One-way analysis of variance with treatment sequence as factor.

b. Fisher exact test p-value (2-tail).

Previous and Concomitant Medication:

Gelusil Usage: A total of 46 of the 76 subjects (61%) took concomitant Gelusil antacid during the study. There were no statistically significant ($p=0.736$) differences between treatments in antacid use.

Non-antacid Concomitant Therapy: Excluding antacids, 43 of the 76 subjects received some type of concomitant therapy during the study. The use of concomitant medications was generally low for both treatment groups. Anilides (eg, acetaminophen) were the only concomitant medications used by more than 15% of subjects in either treatment group. Anilides were used by 17% to 18% of subjects in each treatment group. However, use of these concomitant therapies was also high before the start of the study.

Treatment Compliance:

Subject treatment compliance was assessed at the study site by a count of the test article. The last dose of test article was administered at the study site. In addition, the dose schedule was tracked by information recorded on the CRF (verbal information and review of medication diary).

Treatment compliance was 71% for 1 subject (332-006-0118) in period 1, 86% for 2 subjects (332-005-0167 and 332-006-0092) in period 1, 86% for 2 subjects (332-002-0018 and 332-005-0080) in period 2, and 100% for the remaining subjects. There were no exclusions based solely on compliance.

Analytical Method Development and Validation: The principle of the analytical method used was the titration of the gastric secretion to a pH of 7.0 to measure Total Titrable Acidity, the amount of free HCL plus all other acids contained in the sample (including bound H+ such as protein). Calculate the Total Acid (mEq) {= Acid concentration (mEq/L) x Total gastric sample volume (mL)} x 4 (aliquots obtained over 60 minutes).

Acid Concentration (mEq/L) = Volume of NaOH (mL) x Concentration of NaOH (meq/L)/Volume of gastric sample titrated (mL) L x 1000mL

Biological Matrix	Analytical Site	Method Validation		Method	Sensitivity	Study Number	In-Process Assay Reference(s)
		Reference	Analyte(s)		Linear Range (ng/mL)		
Gastric secretion		Laboratory Test #082214 ^a (See Appendix 1)	Gastric acid <i>plasma</i>	pH Titration, Total Acidity	pH 1.68 to 7.00	3001B1-332-US	Report 03-14-01 (see Appendix 2)

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Table 3.1-3: Summary of Results of In-Process Titration Acid QC Standard for Total Acid for Basal Acid Output (BAO) and Maximum Acid Output (MAO) Assays

Protocol Number	Analyte	Standard Assay Preparation	Standard mEq/L	n ^a	Volume (mL) of 0.1N NaOH to Neutralize Acid Standard (Mean±SD)	Calculated mEq/L (Mean ± SD)	Precision (%CV)	Accuracy (% Bias)
3001B1-332-US	Intra-assay 0.1N HCl Acid Standard	1 mL 0.1N HCl diluted with 9 mL water	100	20	1.0501±0.0129	105.01±1.29	1.2	NA
	Inter-assay 0.1N HCl Acid Standard	1 mL 0.1N HCl diluted with 9 mL water	100	19	1.0470±0.0104	104.70±1.04	1.0	NA

^aNumber of assays

Reviewer's Comments: The method is not acceptable. The analytical method validation was inadequate. In addition, an audit by the Division of Scientific Investigations (DSI) of the analytical portions of the pharmacodynamic comparability study (# 3001B1-332-US). The audit found that the analytical data for the primary pharmacodynamic endpoint (MAO) was not acceptable for review. Therefore the data obtained is not reliable.

Results of Efficacy Evaluations:

Sequence	Statistics	Period 1 (Days 6-8)	Period 2 (Days 6-8)
Sequence I		Spheroid 40 mg	Tablet 40 mg
	N	28	28
	Mean ± SD	7.16 ± 5.07	7.54 ± 4.80
	Median	6.77	7.00
	Min, Max	0.56, 21.42	0.58, 18.96
Sequence II		Tablet 40 mg	Spheroid 40 mg
	N	24	24
	Mean ± SD	7.01 ± 4.82	7.04 ± 4.99

	Median	5.35	6.47
	Min, Max	1.68, 18.81	0.70, 23.62
Abbreviations: SD=standard deviation; Min=minimum; Max=maximum.			

Table 9.4.1.1-3: Statistical Analysis for Maximum Acid Output (mEq/h) (Spheroid 40 mg - 1.2 × Tablet 40 mg)

Analysis Population	N	Mean	SD	Median	t-Test	p-Value	
						Rank Test	Normality
ITT	71	-2.73	4.73	-2.21	0.000	0.000	0.283
mITT	52	-1.65	4.61	-1.34	0.006	0.002	0.104
VFE	51	-1.57	4.62	-1.33	0.010	0.003	0.091

Abbreviations: SD=standard deviation; ITT=intent-to-treat; mITT=modified intent-to-treat; VFE=valid for Efficacy

Applicant's Conclusions:

For the mITT population, the comparability of the MAO_{spheroid} and the MAO_{tablet} was established by rejecting the null hypothesis that they differed by more than 20% (p=0.006, t-test). The assumption of normality for MAO was not rejected; the p-value from the one-sided t-test was reported. These results demonstrate that the maximum acid output for the spheroid 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.

Reviewer's Comments: The data above does not demonstrate PD comparability because the statistical method used is a non-inferiority test and not a comparability test. To show comparability, the applicant needed to do a 2-sided t-test. In addition, the reliability of the data cannot be established due to the inadequacy of the analytical method validation.

Secondary Efficacy Endpoints:

Treatment	Number of Subjects	MAO	BAO	Median Intraesophageal pH	Median Intra gastric pH
Delayed-release granules 40 mg ^a	52 ^b , 53 ^c	7.11 ± 4.98	0.74 ± 0.91	5.62 ± 0.56	4.39 ± 1.02
Delayed-release tablet 40 mg ^a	52 ^b , 53 ^c	7.29 ± 4.77	0.58 ± 0.63	5.57 ± 0.52	4.11 ± 1.19

Abbreviations: BAO = basal acid output; MAO = maximum acid output; mITT = modified intent-to-treat; SD = standard deviation. a. Values are expressed as the mean ± SD. b. Number of subjects for MAO and BAO in mITT. c. Number of subjects for median intraesophageal pH and median intra gastric pH in mITT.

that the mean BAO (mEq/h) with the spheroid formulation was more than 20% of the mean BAO with the tablet formulation.

Applicant's Conclusions:

- The MAO for the 2 formulations of 40 mg pantoprazole was 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).

Reviewer's Comments: It should be noted that the mean BAO for the granules was higher than that obtained with the tablets and this was statistically significant

- 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.

Study # 3001-B1-116US

Title: 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

Study Objective(s) Primary: To determine the bioequivalence of the to-be-marketed formulation dosed orally in 3 different regimens (sprinkled on applesauce, mixed with apple juice, and administered through a nasogastric [NG] tube with apple juice). **Secondary:** To obtain additional safety and tolerability data of pantoprazole in healthy subjects.

Study period: 16 May 2005 to 28 May 2005 (Plasma sample analysis was from May 27th, 2005 to June 8th, 2005)

Study Design This is an open-label, randomized, 3-period, 6-sequence, crossover, single-center study in healthy subjects.

Study Population: ~25 healthy subjects enrolled and completed

Test Article: Pantoprazole 40 mg enteric-coated delayed release granules in capsules (Batch Number: 2005B0001 Formulation Number: 0932097V)

Dosage and Administration Each subject will receive single doses of the commercial formulation of pantoprazole under fasting conditions. Each single dose will be separated by a washout interval of at least 1 day. Subjects will be randomly assigned to 1 of 6 of the following treatment sequences: ABC, BCA, CBA, ACB, BAC, CAB

A: Single dose of pantoprazole spheroids sprinkled over applesauce.

B: Single dose of pantoprazole spheroids mixed with apple juice.

C: Single dose of pantoprazole spheroids mixed with apple juice and administered through an NG tube.

All treatments will be preceded by an overnight fast of at least 10 hours.

Pharmacokinetics: Blood samples will be obtained to determine the PK of each regimen.

Blood samples (5 mL) will be obtained within 2 hours before test article administration and 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. A noncompartmental PK method will be used to analyze the plasma concentrations of pantoprazole.

Bioanalytical Methodology: Plasma samples were analyzed for pantoprazole concentrations by a validated LC-MS-MS method. The limit of quantitation was 10 ng/mL and the assay was linear up to 5000 ng/mL using 0.1 mL of plasma.

Statistical Analysis: The statistical analysis will consist of computation of the geometric means and ranges of estimates of the primary PK parameters (C_{max}, AUCT, and AUC), and comparison of the parameter estimates between the test and reference treatments, which are pantoprazole sprinkled on applesauce (reference treatment) and pantoprazole mixed with apple juice, and pantoprazole mixed with apple juice and dosed through an NG tube (test treatments). The comparison will be made using an analysis of variance. Additionally, least square geometric mean and 90% confidence limits for the test-to-

reference ratios of the primary parameter estimates (Cmax, AUCT, and AUC) will be constructed on the log scale using the 2, 1-sided test procedure. The test and reference treatments will be judged to be bioequivalent if the 90% confidence limits fall within the bioequivalence interval (0.80, 1.25).

Results:

Subjects Excluded From the Pharmacokinetic Analysis: Subjects 0005, 0016, and 1005 were excluded from statistical analysis as their NG tube was found to be clogged and total dose was not delivered into the stomach. A report from the site monitoring visit from 22 Jun 2005 was attached that reflects the issues related to these 3 subjects.

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Table 7.2-1: Demographic and Other Baseline Characteristics			
Protocol No:	Identity of Subject Population:		Study Status:
3001B1-116-US	Safety		Completed
Demographic Characteristic	-----Number of Subjects-----		
	Enrolled	Completed	Discontinued
Total	25	25	0
Sex			
Male	25		
Female	0		
Mean age, years	34.52 ± 8.33		
Age range			
<18 years	0		
18-45 years	23 (92%)		
46-64 years	2 (8%)		
>64 years	0		
Ethnic origin			
Black	17 (68%)		
White	7 (28%)		
Other	1 (4%)		

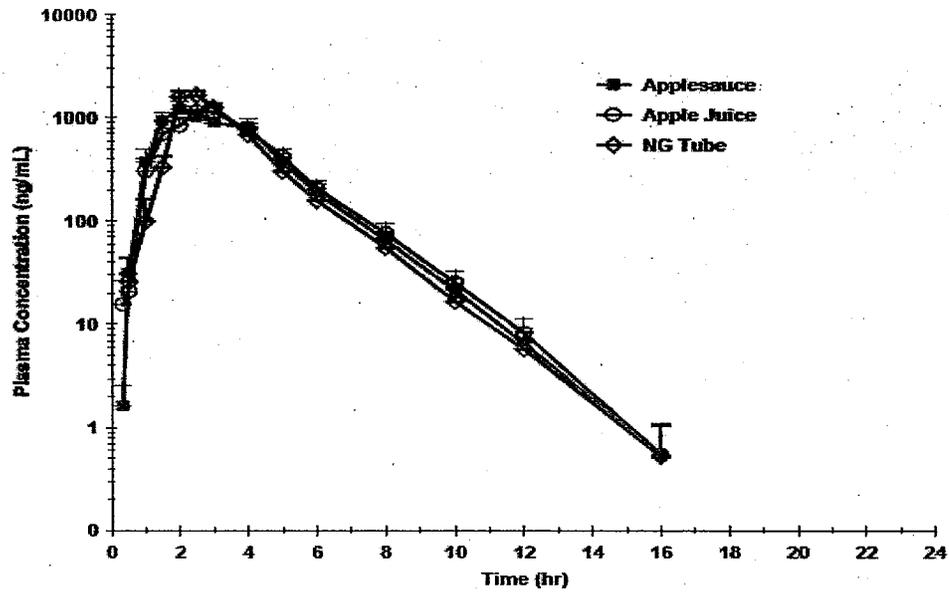
Concomitant Therapy

Three subjects reported non-study medications. Subject 0019 received normal saline, subject 0021 took Benadryl, Zithromax, Tussin DM, and Protonix (on days 6 and 7 for treatment of esophageal irritation and after the PK sampling); and subject 0023 received Cetacaine and Protonix (after treatment for throat irritation).

Pharmacokinetic Results:

Plasma Concentration-Time Profiles:

Figure 8.1.1-1: Mean (SE) Plasma Concentration Time Profiles Following Administration of 40 mg Pantoprazole Sodium Delayed-Release Granules to Healthy Adult Subjects (n=22)



Pharmacokinetic Parameters:

Table 8.1.1-1: Summary of Pharmacokinetic Parameters for Pantoprazole Granules Administered Orally in 3 Different Methods

Regimen ^a	C _{max} (ng/mL)	t _{lag} (h)	t _{max} (h)	AUCT (ng.h/mL)	AUC (ng.h/mL)
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 ^b (GAJ)	101.97	---	---	100.05	100.42
Geometric mean ratio ^c (GNG)	113.39	---	---	99.96	99.94
(GNG) 90% CI ^b (GAJ)	92.4 – 112.5	---	---	94.4 – 106.1	94.8 – 106.4
90% CI ^c (GNG)	102.7 – 125.2	---	---	94.3 – 106.0	94.3 – 105.9

a: Values are expressed as mean \pm SD, except for tlag and tmax for which medians are reported. b: Ratio of granules in apple juice to applesauce. c: Ratio of granules in NG tube to applesauce

Justification for Excluding the Three Subjects from BE Testing

The three subjects in question (#s 0005, 0016 and 1005) were originally 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 (refer to CSR-61354 section 7.1.3). We also noted in CSR-61354 section 7.1.3: "A report from the site monitoring visit from 22 Jun 2005 is attached that reflects the issues related to these 3 subjects." We inadvertently did not create a hypertext link that would take a reviewer directly to the referenced attachment. Consequently, the attachment was not included in the original study report.

We attach herewith, two reports from the site monitoring visits that were conducted on 24 May 2005 and 15 June 2005. These reports constitute the attachment that was referenced but inadvertently not included in the original study report (CSR-61354 section 7.1.3). The report of the site monitoring visit dated 24 May 2005 (refer to the narrative section of the report) indicated that Subject #0005 was replaced because the subject's "3rd dose (spheroids via NG tube) was not able to be completed due to the blocking of the NG tube with the spheroids". Similarly, the report of the site monitoring visit dated 15 June 2005 (refer to the narrative section of the report) noted: "Subject 1005 was dosed to replace subject 0005 because the NG dosing was problematic (clogging of the NG with spheroids)." Furthermore, "there were 2 subjects in this group that also had a blockage with their NG dosing with spheroids. Subject 0016 and 1005 had 'too numerous to count' spheroids in their NG tubes on examination".

Reviewer's Comments: This justification indicates that clogging of the NG tube may be a problem during actual use. In addition, The 90% CI's for the ratio of the geometric means for C_{max} , AUC_T , and AUC , of the granules delivered via nasogastric (NG) tube to granules in applesauce were not within the BE limits of 80-12% when these three subjects are included in the analysis.

Applicant's Discussion:

For the primary PK parameters C_{max} , AUC_T , and AUC , the 90% CI's for the ratios of the geometric means of the delayed release granules in apple juice or the granules administered through NG tube, relative to the granules administered with applesauce, were within the BE limits of 80%-125%. Therefore pantoprazole delayed release granules administered with apple juice and through NG tube are bioequivalent to granules administered with apple sauce. For C_{max} , the ratio of the geometric means of the delayed release granules administered through NG tube reached the upper bioequivalence limit of 125% (125.15). This is probably because NG tube prevents wide distribution of the granules along the GI tract resulting in slightly higher C_{max} values compared to granules administered with applesauce or apple juice.

In conclusion, the pharmacokinetic results from the present study showed that the to-be-marketed formulation of pantoprazole delayed release granules can be administered either with apple juice or with apple juice through NG tube, as both the methods of administration are bioequivalent with the granules administered with applesauce.

Reviewer's Comments: Administration through the NG tube may not be interchangeable due to problems with clogging of the tube.

Analytical Methods and Validation:

Appears This Way
On Original

TABLE 1
Summary of Results and Conclusions of the Bioanalytical Method Validation
Analyte: Pantoprazole

	Acceptance Criteria	Method Performance
Methodology		LC/MS/MS
Instrumentation		Type 3: Liquid/Liquid, organic transfer, complete dryness
Extraction		100 µL
Plasma Volume		
Specificity		Human plasma
Matrix		Sodium Heparin
Anticoagulant		
Pantoprazole:		
Model		$y = a + bx$
Weighing		$1/x^2$
Linearity		≥ 0.994
Correlation Coefficient (r^2)		0.17%
% Recovery LLOQ		-5.42 to 5.10%
% Recovery above LLOQ		10.00-5000.00 ng/mL
Analytical Range		10.00 ng/mL
Sensitivity (LLOQ)		0.32% (LLOQ); -0.76 to 4.96% (Above LLOQ)
Accuracy (Among Batch)		-13.65 to 12.13% (LLOQ); -3.15 to 10.93% (Above LLOQ)
Accuracy (Within Batch)		11.81% (LLOQ); 3.45 to 7.15% (Above LLOQ)
Precision (Among Batch)		4.86 to 9.48% (LLOQ); 2.16 to 7.55% (Above LLOQ)
Precision (Within Batch)		
Stability		
Freeze/Thaw (human plasma; -20 °C/37 °C)		4 cycles – complies
Freeze/Thaw (human plasma; -20 °C/Room Temperature)		3 cycles – complies
Room Temperature (plasma; 25 °C)		4.50 hours
Autosampler (extract; 25 °C)		102.77 hours for pantoprazole
Refrigerator (extract; 4 °C)		103.98 hours for pantoprazole
Long-Term (plasma; -20 °C)		44 days
Whole Batch Reinjection Integrity		291.65 hours
Individual Sample Reinjection Stability		10.32 hours
Dilution (x2)		Complies
Matrix Effect	accuracy: \rightarrow accuracy and precision precision	Complies
Extraction Recovery (Pantoprazole)		~ 87%
Extraction Recovery (Omeprazole; IS)		~ 90%
Solution Stability		
Pantoprazole		
100 µg/mL primary (4 °C)		6 months (V1879P1)
100 µg/mL primary (6 hour, 25 °C)		Complies (V1879P1)
100 µg/mL primary (4 °C)		9 months (V1292P1)
100 µg/mL primary (6 hour, 25 °C)		Complies (V1879P1)
		4 months (V2191P1)
		Complies, (V2191P1)
System Verification Solution		44 days (V2191P1)

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Three cycles of human heparin plasma freeze/thaw (-20 °C/Ambient), four cycles of human heparin plasma freeze/thaw (-20 °C/37 °C) stability and three cycles freeze/thaw (-70 °C/37 °C) stability, 4.5-hour benchtop stability, and extracted sample stability (103.98-hours at refrigeration temperature) were established in V2191P1. Long-term stability of pantoprazole in human plasma has been established for 29 months at -70 °C as reported in *V1265P1 addendum (find this)*. Sample analyses were begun on 27May2005 and were completed on 8Jun2005.

Synopsis of the Initial Comparative Bioavailability of the Pilot Granule Formulation to the Marketed Tablet: Study 3001A1-114-US
 The primary objective of study 3001A1-114-US was to assess the relative bioavailability of a pilot pantoprazole sodium granule formulation (pilot formulation) administered using 2 different delivery methods and the currently marketed tablets of pantoprazole in healthy adult subjects.

The secondary objective of this study was to provide the initial PK profile of the pantoprazole sodium granules administered by using 2 different dosing administration methods in healthy subjects. In this open-label, 3-period, crossover study, a single 40 mg oral dose of test article was administered to healthy subjects after an overnight fast of at least 10 hours on study day 1 in each of the 3 periods. Each subject was randomized to receive 1 dose of pantoprazole in each period as either 40 mg of pantoprazole sodium delayed-release granules sprinkled on applesauce (1 tablespoon), 40 mg of pantoprazole sodium delayed release granule suspension (inactive powder blend mixed with 5 ml distilled water), or the marketed 40-mg pantoprazole tablet. All administered doses were followed by 240 mL of room temperature water.

Results:

Twenty-four (24) of the 26 subjects enrolled in the study completed all 3 treatment periods. Two (2) subjects were withdrawn from the study after completing 2 treatment periods; they did not receive a dose of pantoprazole in period 3. A summary of the PK parameters for pantoprazole is shown in the below.

Table 2.2.1.1-1: Pharmacokinetic Parameters for Pantoprazole: Study 3001A1-114-US Mean ± SD^a (n=24)

Formulation	C _{max} (ng/mL)	t _{max} (h)	t _{lag} (h)	AUCT (ng.h/mL)	AUC (ng.h/mL)
Tablet	2958 ± 927	2.5	1.5	5810 ± 5287	6073 ± 6146
Granules sprinkled on applesauce	1865 ± 708	2.5	0.2	5168 ± 4891	5451 ± 5845
Granule suspension	1929 ± 550	2.0	0.3	5408 ± 4947	5629 ± 5653

Abbreviations: C_{max} = peak concentration; AUCT = area under the concentration-time curve to the last observable concentration (CT) at time T; AUC = total area under the concentration-time curve; SD = standard deviation; t_{max} = time peak concentration occurs. a. Median values reported for t_{max} and t_{lag}.

Applicant's Discussion:

The plasma AUC for the granules sprinkled on applesauce or given as a suspension was similar to that for the tablet formulation, with C_{max} being lower for the delayed-release granules. The lower C_{max} with the granules was anticipated, based on the way each formulation travels through the gastrointestinal tract. A lag time was seen with the tablet. It appears that once the tablet reached the small intestine, it dissolved, releasing the drug over a short time interval, and yielding a relatively high concentration of the drug at the site of absorption (the small intestine). With the granules there was essentially no lag time. It is conceivable that granules can be dispersed rapidly and relatively evenly along the gastrointestinal tract in a manner less dependent of gastric emptying than the intact tablet. As a result, the drug release/absorption phase for the granules is longer, resulting in a flatter plasma concentration-time curve (lower C_{max}), as compared to the tablet. For AUC, the 90% confidence interval (CI) for the ratios of the geometric means of the granules sprinkled on applesauce to the tablet was 84.7% to 95.9% and for the pantoprazole sodium granule suspension to the tablet was 88.1% to 99.8%; both of these sets of confidence intervals were within the bioequivalence limits of 80% to 125%. For C_{max}, the 90% CI was 55.6% to 70.0% for the ratio of granules sprinkled on applesauce to tablet and was 58.9% to 74.1% for the ratio of granule suspension to tablet. The pantoprazole sodium delayed-release granules did not meet the criteria for bioequivalence limits for C_{max}.

4.4 OCPB Filing Form:

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA Number	22-020	Brand Name	Protonix ® Delayed-Release Σ \square
OCBP Division (I, II, III)	DCP3	Generic Name	Pantoprazole Sodium
Medical Division	HFD-180	Drug Class	Proton Pump Inhibitor (PPI)
OCBP Reviewer	Abi Adebowale	Indication(s)	Alternative to the marketed tablet formulation for patients who are unable to swallow the tablet for the treatment of gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis
OCBP Acting Team Leader	Tapash Ghosh	Dosage Form	Delayed-Release Granules
Letter Date	July 17th, 2006	Dosing Regimen	40 mg once daily for up to 8-weeks. An additional 8 weeks treatment may be considered for patients who are not treated after 8 weeks
Stamp Date	May 12th, 2006	Route of Administration	Oral
Estimated Due Date of OCPB Review	February 28th, 2007	Sponsor	Wyeth Pharmaceuticals
PDUFA Due Date	March 15th, 2007	Priority Classification	3S
Clinical Division Due Date	February 22 nd , 2007	IND Number	68,011 Related NDAs: 20-987

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	3		RPT-54260, Laboratory Test # 082214, GTR-30693
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				

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Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	1		3001B1-332-US
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference (IR):				
Bioequivalence studies -	X	2		3001-B1-116-US (BE of dosing regimens) and 3001-A1-114-US (pilot granules)
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		3001-A1-115-US and 3001A1-118-US (pilot granules)
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5		
Filability and QBR comments				
Types and #'s of studies and supplementary information (literature review) are adequate to conduct a review	"X" if yes X	Comments: DSI –bioequivalence consult was requested		
Application filable?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?	Yes	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Is the granule BE to the Tablets? Is the PD comaparability study acceptable in lieu of the BE study?			

Other comments or information not included above	This was inherited from Suliman in October.
Primary reviewer Signature and Date	Abi Adebawale 01/18/07
Secondary reviewer Signature and Date	

CC: NDA 22-020, HFD-850 (P.Lee), HFD-180 (T.Moreno), DCP 3 (D. Bashaw, A.Adebawale, T.Ghosh)

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/s/

Abi Adebawale
3/6/2007 05:35:44 PM
BIOPHARMACEUTICS

Tapash Ghosh
3/7/2007 09:10:15 AM
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