

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-020**

**CHEMISTRY REVIEW(S)**



Chemistry Assessment Section

**Memorandum**

Date: Nov 14, 2007  
From: Zhengfang Ge, Ph.D., Reviewer  
Through: Moo-Jhong Rhee, Ph.D., Branch Chief  
To: NDA 22-020  
Subject: Addendum to Review #1 regarding Labeling

The package insert has been reviewed for NDA 22-020. The nomenclature for the dosage form has been changed to "For Delayed-Release Oral Suspension" based on the agreement between the Agency and the sponsor during the 1<sup>st</sup> review circle. The sponsor also accepted the wording to emphasize that the drug product should not be prepared in water or other liquids (only in apple juice or apple sauce). Some other minor wording was also modified. From CMC prospective, the final labeling is satisfactory and this NDA can be approved.

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/s/

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Zhengfang Ge  
11/14/2007 11:32:34 AM  
CHEMIST

Moo-Jhong Rhee  
11/14/2007 02:38:58 PM  
CHEMIST  
Chief, Branch III

**NDA 22-020**

**Protonix (pantoprazole sodium) For Delayed-Release Oral  
Suspension, 40 mg  
Wyeth Pharmaceuticals**

**Division of Gastroenterology**

**Zhengfang Ge, Ph.D.**

**Branch III, Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment**



# Chemistry Review Data Sheet

1. NDA # 22-020
2. REVIEW # 1
3. REVIEW DATE: Feb 28, 2007
4. REVIEWER: Zhengfang Ge

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original submission

May 12, 2006

Amendment (BC)

June 30, 2006

Amendment (BC)

July 5, 2006

Amendment (SU)

Oct 13, 2006

Amendment (BL)

Nov 30, 2006

Amendment (BC)

Dec 20, 2006

Amendment (BZ)

Feb 16, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:

Wyeth Pharmaceuticals, Inc

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Address: 500 Arcola Rd  
Collegeville, PA 19426  
Representative: Jethro Ekuta  
Telephone: (484) 865-7408

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Protonix Delayed-Release    
b) Non-Proprietary Name (USAN): Pantoprazole Sodium   
c) CAS No: 138786-67-1  
d) Code Name/# (ONDQA only): None  
e) Chem. Type/Submission Priority (ONDQA only):  
• Chem. Type: 3  
• Submission Priority: S

b(4)

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505(b)(1) of Federal Food, Drug and Cosmetic act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY: proton pump inhibitor

11. DOSAGE FORM: Granules for oral suspension

12. STRENGTH/POTENCY: 40mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

**CHEMISTRY REVIEW**

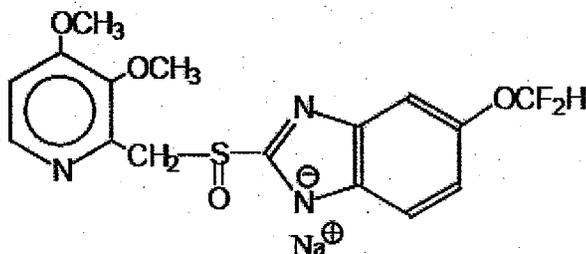
Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Name:**

Sodium-[5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridyl)-methyl]-sulfinyl]-1H-benzimidazole sesquihydrate

**Molecular Formula:** C<sub>16</sub>H<sub>14</sub> F<sub>2</sub>N<sub>3</sub>NaO<sub>4</sub>S x1.5 H<sub>2</sub>O



**Molecular Weight:** 432.4 (includes water)

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TY PE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLET ED	COMMENTS
[ ]	II	Altana Pharma	Drug substance manufacturer	1	Adequate	Nov 16, 2006	Reviewed for this NDA
[ ]	II			1	Adequate	Nov 16, 2006	Reviewed for this NDA
[ ]	II			1	Adequate	Nov 16, 2006	Reviewed for this NDA
[ ]	III			4	N/A		Sufficient information provided

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Initial Quality Assessment	NDA 22-020	Nov 1, 2006
Reviews	NDA 20-987	Original NDA and supplements
Reviews	NDA 20-988	Original NDA and supplements

## 18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	24-Jan-2007	Office of Compliance
Pharm/Tox	Not Applicable		
Biopharm	Not Applicable		
LNC	Not Applicable		
Methods Validation	Not needed at this time		
DMETS	Pending		
EA	Adequate		Section II/B of this review
Microbiology	Not applicable		

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# The Chemistry Review for NDA 22-020

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From CMC point of view, this NDA can be approved pending resolution of some labeling issues.

#### 1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Substance:

The drug substance is pantoprazole sodium sesquihydrate with a molecular formula of  $C_{16}H_{14}F_2N_3NaO_4S \times 1.5 H_2O$  and molecular weight of 432.4. This is the same drug substance that is used in PROTONIX (Pantoprazole Sodium) Delayed-Release Tablets, which is approved under NDA 20-987. It will be obtained from the same suppliers (Altana Pharma, ) and will conform to the same specifications as approved in NDA 20-987. Reference is made to DMFs    as well as NDA 20-987 for all Chemistry, Manufacturing and Controls information related to the drug substance. Updates of the DMFs are reviewed separately and are adequate.

##### Drug Product:

The drug product is granules for delayed-release oral suspension. It was developed to facilitate oral administration of pantoprazole to   adult patients who have difficulty swallowing. The product is formulated to deliver a 40 mg dose of pantoprazole after suspended in apple juice or applesauce through oral administration and apple juice suspension through nasogastric tube. The product is packaged in unit-dose child-resistant packet

A box of 30 packets will be marketed.

Each unit packet of the drug product consists enteric-coated granules containing 45.1 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg of pantoprazole) and the following inactive ingredients: crospovidone, hypromellose, methacrylic acid

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

copolymer, microcrystalline cellulose, polysorbate 80, povidone, sodium carbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate, and yellow ferric oxide. All excipients conform to USP/NF monograph requirements. Methacrylic acid copolymer [ ] It is the [ ] that is used in PROTONIX Delayed-Release Tablets. Polysorbate 80 [ ] making the granule formulation pharmacodynamically comparable to the approved 40 mg tablets. The pantoprazole granule [ ] [ ]

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The review of this drug product is based on the approved tablet and IV drug products. The current granule drug product specification is in general similar to the tablet and IV products. A new degradant is identified in this product. Its identification and specification are provided and are acceptable. The specification for total impurity is [ ] the approved specification for the tablets and IV products and is [ ] comparing to the batch results, therefore, the sponsor was asked [ ] specification to NMT [ ]

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Based on the results of 12 months of controlled room temperature (25°C/60%RH) stability data and 6 months of accelerated (40°C/75%RH) stability data, as well as up to 24 month statistically simulated stability results under controlled room temperature, the proposed expiration period of 18 months under room temperature storage is acceptable.

Satisfactory recommendation from facility inspections in the manufacture of the drug substance and drug product was reached on 24-Jan-2007.

The sponsor proposed to use [ ] for the dosage form. In order to be consistent with the previously approved similar products, the sponsor was requested to change the dosage form to "For Delayed-Release Oral Suspension". Also, the sponsor was requested to [ ] [ ]

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**B. Description of How the Drug Product is Intended to be Used**

The drug product is indicated for 1) short term treatment of erosive esophagitis associated with GERD 2) maintenance of healing of erosive esophagitis and 3) pathological hypersecretory conditions including Zollinger-Ellison Syndrome

## Chemistry Assessment Section

The drug product is orally administered with suspension in apple juice or apple sauce. The apple juice suspension can also be administered through nasogastric tube for the patients who have a nasogastric tube in place.

**C. Basis for Approvability or Not-Approval Recommendation**

The drug substance is the same one used for the approved delayed-release tablets. The CMC information for the drug substance is cross referenced to 2 DMFs, which are found adequate, and the approved NDA for the tablets. Therefore, the drug substance is adequate. Review of this NDA found that the sponsor provided adequate CMC information regarding composition, manufacturing process and process controls for the drug product. The updated stability data is adequate to support 18 months of expiring date. The sponsor accepted the Agency's requests regarding the specification for the total degradation products and the established name. Overall acceptable recommendations were reached for the inspections at the manufacturing facilities on 24-Jan-2007. From CMC prospective, the NDA can be approved except that some minor wording in the labeling insertion needs to be corrected in the next review circle since no labeling insertion review is conducted for this NDA because of non-approval issue from clinical prospective.

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**III. Administrative****A. Reviewer's Signature**

*In DFS*

**B. Endorsement Block**

Chemist: Zhengfang Ge  
Chemistry Branch Chief: Moo-Jhong Rhee  
ProjectManager: Tom Moreno

**C. CC Block**

37 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Zhengfang Ge  
2/28/2007 02:24:03 PM  
CHEMIST

Moo-Jhong Rhee  
3/2/2007 01:47:25 PM  
CHEMIST  
Chief, Branch III

Initial Quality Assessment  
Branch 3  
Pre-Marketing Assessment Division 2

**OND Division:** Division of Gastroenterology Products  
**NDA:** 22-020  
**Applicant:** Wyeth  
**Stamp Date:** 5/15/06  
**PDUFA Date:** 3/15/07  
**Trademark:** Protonix®  
**Established Name:** Pantoprazole sodium  
**Dosage Form:** Delayed Release Granules  
**Route of Administration:** oral  
**Indication:** Proton pump inhibitor

**PAL:** Marie Kowblansky, PhD

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

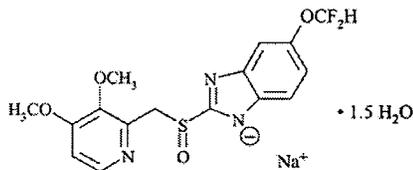
### A. Summary

PROTONIX® (pantoprazole sodium) Delayed-Release  was developed to facilitate oral administration of pantoprazole to pediatric patients and adult patients who have difficulty swallowing. The product is formulated to deliver a 40 mg dose of pantoprazole after dispersion in apple juice or applesauce. Even for nasogastric tube administration, label instructions call for dispersing the product in apple juice, not water. The product is packaged in unit-dose child-resistant

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### Drug Substance

The active drug substance in this product is pantoprazole sodium sesquihydrate



This is the same drug substance that is used in PROTONIX (Pantoprazole Sodium) Delayed-Release Tablets, which is approved under NDA 20-987. It will be obtained from the same suppliers (Altana Pharma,  and will conform to the same specifications as approved in NDA 20-987. Reference is made to DMFs   as well as NDA 20-987 for all Chemistry, Manufacturing and Controls information related to the drug substance.

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### Formulation

Each product packet is filled with enteric-coated granules containing 45.1 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg of pantoprazole) with the following inactive ingredients: crospovidone, hypromellose, methacrylic acid copolymer, microcrystalline cellulose, polysorbate 80, povidone, sodium carbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate, and yellow ferric oxide. All excipients conform to USP/NF monograph requirements.

Methacrylic acid copolymer  that is approved for use in PROTONIX Delayed-Release Tablets. Polysorbate  It is the  comparable to the approved 40 mg Tablet.

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Two different formulations were used in the phase III clinical trials. Although both formulations contained the same components, the relative proportions were considerably different. For example,

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A reformulation was required to improve the stability of the drug substance in the formulation and to make the granule formulation bioequivalent to the marketed Protonix Tablets. The final phase III formulation is the same as the to-be-marketed product.

Manufacture

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Specifications

The product will conform to the specification given in the table below.

Test	Acceptance Criteria
Appearance and Description:	Pale yellowish to dark brownish granules
Strength (HPLC):	<input type="checkbox"/>
Identity (HPLC):	Positive for pantoprazole
Purity (HPLC):	B8401-026 NMT w/w
	B8510-028 NMT w/w
	B8610-014 NMT w/w
	B8810-044 NMT w/w
	BYK 347611 NMT w/w
	Any Unspecified Degradant NMT w/w
Total Degradants	NMT w/w
Uniformity of Dosage Units (Content Uniformity)	Conforms to USP <905>
Dissolution	Conforms to USP <724>
	NMT <input type="checkbox"/> dissolved in 0.1N HCl in 2 hours
	NLT <input type="checkbox"/> (Q) dissolved in phosphate buffer in 45 minutes
Water Content by Loss on Drying	NMT <input type="checkbox"/> <input type="checkbox"/>

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HPLC = High-Performance Liquid Chromatography  
 NLT = Not less than.

NMT = Not more than.

The impurity limits conform to ICH guidance and for the most part are comparable to the limits defined for the approved Protonix tablet and injection products. The only exception is the limit for total impurities, which [redacted] approved for Protonix IV.

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The [redacted] specified degradants, [redacted] were fully identified and characterized in NDA 20-987, PROTONIX (pantoprazole sodium) Delayed-Release Tablets. An additional degradant, [redacted] not observed in the injectable or tablet products, has been identified in the product currently under review. Its structure has been confirmed by IR, NMR and mass spectroscopy.

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Dual Stage Dissolution testing is performed per USP <724>. As indicated in the above table, the limit for pantoprazole is not more than [redacted] release at the conclusion of the 2 hour acid stage test, and not less than [redacted] release in 45 min in the buffer stage (pH 6.8).

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[

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- The measurement of drug release in the buffer stage of the test is also by a non-selective UV Absorbance method, but in this case, [redacted]

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The moisture content limit is set at [redacted] but it should be noted that in the three batches on stability testing, the highest observed moisture content never exceeded [redacted] with most data falling below this value.

#### Packaging

Data are presented for three primary stability batches of the product packaged in [redacted] and considered non-child-resistant. The to-be-marketed container-closure system will be identical to the one used in packaging the stability batches, except that the [redacted]. In the reviewer's opinion, since the packaging configuration is identical and the product contact layer is identical in both packages, [redacted], and consequently, the stability data for product packaged in the [redacted] package is acceptable for consideration of expiration dating of the to-be-marketed product.

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#### Stability and Expiration Dating

Based on the submission of 9 months of controlled room temperature (25°C/60%RH) stability data and 6 months of accelerated (40°C/75%RH) data, the applicant proposes an expiration period of 18 months with room temperature storage. While the data show conformance to all proposed specifications at both storage conditions, [redacted]

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[redacted], an 18-month expiration period may not be justified at the present time. However, the applicant will be submitting additional stability data during the review cycle, which should clarify whether an 18-month expiration period is appropriate.

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In-use Stability

Since administration instructions call for suspension of the product in applesauce or apple juice prior to administration, the stability of the granules was studied in these administration vehicles by measuring the pantoprazole content. Pantoprazole was shown to be stable for up to 2 hours, in both apple juice and applesauce, showing well over 90% of the original content.

Environmental Assessment

Wyeth Pharmaceuticals claims categorical exclusion from preparing an environmental assessment per 21CFR §25.31(b); the substance at the point of entry into the aquatic environment will be below 1 part per billion after metabolism of pantoprazole is considered. Dr. Raanan Bloom of OPS has confirmed that this indeed qualifies for categorical exclusion.

Inspection Requests

Inspections have been requested for all facilities involved in the manufacture of the drug substance and drug product. (See appended list.)

**B. Critical issues for review**

The applicant has significant experience with the drug substance in that they have two other approved Protonix products. Therefore, there are no immediate concerns with the drug substance. The following issues with the drug product may need closer evaluation:

Particle size

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Dissolution testing:

At the end of acid-stage testing, ┌

└

└ While the proposed

general approach is reasonable in view of the instability of pantoprazole under acidic conditions (and any of the pantoprazole dissolved in the acidic medium would be degraded at the end of the two hour testing period), the validation of this method should be carefully evaluated to ensure that the Absorbance is measured when the samples are completely degraded with no additional changes in the Absorbance of the reference or sample.

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The buffer-stage dissolution test is based ┌

└

└ An assay specific for pantoprazole would be

preferred for this purpose. A determination should be made why a specific assay is not being used. If a specific assay is not possible, a careful determination should be made that there are no interferences from other formulation components in the proposed UV test.

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All data from buffer stage testing show at least { } dissolution in 45 minutes, yet the specification requires not less than { } The applicant should be requested to provide a few representative entire dissolution profiles to make a determination whether the { } dissolution specification is appropriate.

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All dissolution data for acid stage testing are presented as a pass/fail. The actual dissolution values should be submitted for the purpose of evaluating the proposed acceptance criterion and the proposed method.

Moisture content:

The need for the — moisture limit is not apparent when no batch data, either initially or on stability testing, showed the moisture content to be more than C → The high limit is of particular concern since the applicant acknowledges in the submission that preliminary stability studies showed that the product to be moisture sensitive.

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In use stability

Although the submission provides data demonstrating the chemical stability of pantoprazole after suspension of the product in apple juice and applesauce, it may be useful to also determine the dissolution properties of the product after 2-hour suspension in the apple vehicles.

Although the product administration directions call only for suspension in applesauce or apple juice, it may be useful to request dissolution data in water, to understand if labeling would require a prominent precaution that the product should not be suspended in water.

Established name

The proposed product name is PROTONIX® (pantoprazole sodium) Delayed-Release C → However, by analogy to recently approved similar products, the name

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PROTONIX® (pantoprazole sodium) for Delayed-Release Oral Suspension

would likely be more appropriate.

**C. Comments for 74-Day Letter -- None**

Marie Kowblansky, PhD  
Pharmaceutical Assessment Lead

11/1/2006  
Date

Moo-Jhong Rhee, PhD  
Branch Chief

11/1/2006  
Date

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MANUFACTURING FACILITIES

Drug product manufacturing, primary and secondary packaging, labeling, analytical release testing and stability testing of the commercial finished product.

ALTANA Pharma Oranienburg GmbH  
Lehnitzstrasse 70-98  
D-16515 Oranienburg Germany  
Facility Establishment Identifier: 3003729907

The drug substance will be provided by — alternate suppliers:

Altana Pharma (DMF C 3)  
ALTANA Pharma AG  
Robert Bosch Strasse8  
D- 78224 Singen,  
Germany

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Moo-Jhong Rhee  
11/8/2006 11:22:59 AM  
CHEMIST  
Chief, Branch III