

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-987

CHEMISTRY REVIEW(S)

JAN 28 2000

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS**  
Review of Chemistry, Manufacturing and Controls

NDA: 20-987

Chem. Review: #6

Review Date: 01/28/00

Submission Type	Document Date	CDER Date	Assigned Date
BZ	January 28, 2000	January 28, 2000 (FAX)	January 28, 2000
BZ	December 14, 1999	December 15, 1999	December 17, 1999
AZ	July 30, 1999	August 3, 1999	
BC	October 13, 1999	October 14, 1999	
BZ	September 22, 1999	September 23, 1999	

**Name and Address of Applicant:**

Wyeth Ayerst Laboratories  
P.O. Box 8299  
Philadelphia, PA 19101-8299

**Drug Product Name:**

Proprietary:	PROTONIX™ Tablets
Non-proprietary/USAN and CAS:	pantoprazole sodium
Code Number (CAS):	164579-32-2
Code Number (laboratory):	B8610-23 (Byk-Gulden)
	WAY-140951 (Wyeth-Ayerst code)
Chem. Type/Ther. Class	1S

ANDA Suitability Petition/DESI/Patent Status: N/A

**Pharmacological Category /Indications:**

-proton pump inhibitor

**Dosage Form:** Tablet, enteric-coated

**Strength:** 40 mg

**Route of Administration:** oral

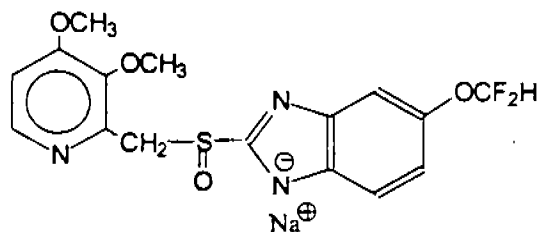
**How Dispensed:**  Rx  OTC

**Chemical Name, Molecular Formula, Molecular Weight, Structural Formula**

**Chemical Name :**

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

**Structure:**



**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)

## Supporting Documents

DMF	SUBJECT	DMF HOLDER	STATUS	REVIEW DATE	LETTER DATE
---	Drug Substance Manufacturer	Byk Gulden	Adequate	4/2/99	2/4/99 4/5/99 10/21/99 11/23/99
---	Supplier	---	Adequate (for tablets)	1/16/98	---
---	High Density Polyethylene (HDPE) Resin	---	Adequate	2/29/97	---
---	Printing Ink Supplier	---	Adequate	4/12/99	---
---	HDPE Bottle Supplier	---	Adequate	9/30/92 (still current)	---
---	HDPE Bottle Supplier	---		Under review (D.Klein)	---
---	HDPE Bottle Supplier	---	Adequate	8/9/99	---
---	Child-Resistant Closure	---	Adequate	4/7/95	---
---	Cap Liner	---	Adequate	4/7/95	---
---	Blister Dome Matenals	---	Adequate	2/17/98	---
---	Aluminum Foil Backing (Lidding)	---	Adequate	7/15/97	---
---	Tamper Evident Seal	---	Adequate	3/13/96	---
---	Non child-resistant caps	---	Adequate	8/13/99	---
---	---	---	Adequate (additional information requested)	9/30/99	9/30/99
---	---	---		Under Review (R. Trimmer)	10/1/99

(NOTE: Other than the above packaging DMFs were cited with the original application. However, the applicant was advised that only those that were used in stability studies would be considered for approval. The above list is the revised list submitted in the July 30<sup>th</sup> submission.)

## Consults:

Biopharm. Review. Approvable 6/28/99. Most recent submission under review by David Udo, Ph.D.  
EER Status: Acceptable, February 5, 1999

Remarks/Comments: See review.

APPEARS THIS WAY  
ON ORIGINAL

**Conclusions and Recommendations:** The application should be approved with a 24 month expiration date.

/S/

Marie Kowblansky, PhD  
Review Chemist, HFD-180

1/28/00

/S/

Liang Zhou, PhD  
Chemistry Team Leader, HFD-180

1/28/00

cc: Orig. NDA 20-987  
HFD-180/Division File  
HFD-180/LTalarico  
HFD-180/MWalsh  
HFD-820/JGibbs  
HFD-180/LZhou  
HFD-180/MKowblansky

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APPEARS THIS WAY  
ON ORIGINAL

JAN 24 2000

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS**

Review of Chemistry, Manufacturing and Controls

**NDA: 20-987**

**Chem. Review: #5**

**Review Date: 01/14/00**

<b>Submission Type</b>	<b>Document Date</b>	<b>CDER Date</b>	<b>Assigned Date</b>
BZ	December 14, 1999	December 15, 1999	December 17, 1999
AZ	July 30, 1999	August 3, 1999	
BC	October 13, 1999	October 14, 1999	
BZ	September 22, 1999	September 23, 1999	

**Name and Address of Applicant:**

Wyeth Ayerst Laboratories  
P.O. Box 8299  
Philadelphia, PA 19101-8299

**Drug Product Name:**

Proprietary:	PROTONIX™ Tablets
Non-proprietary/USAN and CAS:	pantoprazole sodium sesquihydrate
Code Number (CAS):	164579-32-2
Code Number (laboratory):	B8610-23 (Byk-Gulden)
	WAY-140951 (Wyeth-Ayerst code)
Chem. Type/Ther. Class	1S

**ANDA Suitability Petition/DESI/Patent Status: N/A**

**Pharmacological Category /Indications:**

-proton pump inhibitor

**Dosage Form:** Tablet, enteric-coated

**Strength:** 40 mg

**Route of Administration:** oral

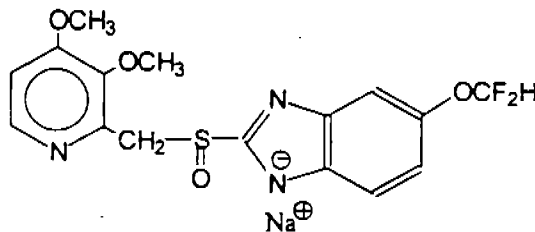
**How Dispensed:**  R<sub>x</sub>  OTC

**Chemical Name, Molecular Formula, Molecular Weight, Structural Formula**

**Chemical Name:**

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

**Structure:**



**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)

**Supporting Documents**

DMF	SUBJECT	DMF HOLDER	STATUS	REVIEW DATE	LETTER DATE
	Drug Substance Manufacturer	Byk Gulden	Adequate	4/2/99	2/4/99 4/5/99 10/21 99 11/23 99
	Supplier		Adequate (for tablets)	1/16/98	----
	High Density Polyethylene (HDPE) Resin		Adequate	2/29/97	----
	Printing Ink Supplier		Adequate	4/12/99	----
	HDPE Bottle Supplier		Adequate	9/30/92 (still current)	----
	HDPE Bottle Supplier			Under review (D.Klein)	----
	HDPE Bottle Supplier		Adequate	8/9/99	----
	Child-Resistant Closure		Adequate	4/7/95	----
	Cap Liner		Adequate	4/7/95	----
	Blistar Dome Matenals		Adequate	2/17/98	----
	Aluminum Foil Backing (Lidding)		Adequate	7/15/97	----
	Tamper Evident Seal		Adequate	3/13/96	----
	Non child-resistant caps		Adequate	8/13/99	----
			Adequate (additional information requested)	9/30/99	9/30/99
				Under Review (R.Trimmer)	10/1/99

(NOTE: Other than the above packaging DMFs were cited with the original application. However, the applicant was advised that only those that were used in stability studies would be considered for approval. The above list is the revised list submitted in the July 30<sup>th</sup> submission.)

**Consults:**

Biopharm. Review. Approvable 6/28/99. Most recent submission under review by David Udo, Ph.D.  
EER Status: Acceptable, February 5, 1999 (see attached report)

**Remarks/Comments:** See review.

**APPEARS THIS WAY  
ON ORIGINAL**

**Conclusions and Recommendations:** The application is approvable pending the addition of moisture specification to the stability testing protocol.

*/S/*

Marie Kowblansky, PhD  
Review Chemist, HFD-180

*1/24/99*

*/S/*

Liang Zhou, PhD  
Acting Chemistry Team Leader, HFD-180

*1/24/2000*

cc: Orig. NDA 20-987  
HFD-180/Division File  
HFD-180/LTalarico  
HFD-180/MWalsh  
HFD-820/JGibbs  
HFD-180/LZhou  
HFD-180/MKowblansky

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APPEARS THIS WAY  
ON ORIGINAL

NOV - 3 1999

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS**  
Review of Chemistry, Manufacturing and Controls

**NDA: 20-987                      Chem. Review: #3                      Review Date: 11/3/99**

<b>Submission Type</b>	<b>Document Date</b>	<b>CDER Date</b>	<b>Assigned Date</b>
AZ	July 30, 1999	August 3, 1999	August 10, 1999
BC	October 13, 1999	October 14, 1999	

**Name and Address of Applicant:**

Wyeth Ayerst Laboratories  
P.O. Box 8299  
Philadelphia, PA 19101-8299

**Drug Product Name:**

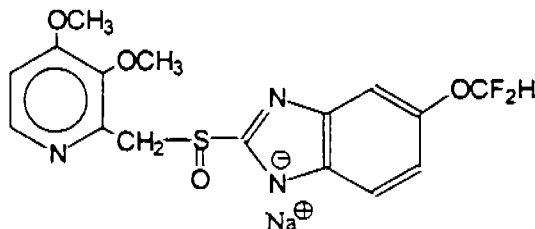
Proprietary:	PROTONIX™ Tablets
Non-proprietary/USAN and CAS:	pantoprazole sodium sesquihydrate
Code Number (CAS):	164579-32-2
Code Number (laboratory):	B8610-23 (Byk-Gulden)
	WAY-140951 (Wyeth-Ayerst code)
Chem. Type/Ther. Class	1S

**ANDA Suitability Petition/DESI/Patent Status: N/A****Pharmacological Category /Indications:**

-proton pump inhibitor

**Dosage Form:** Tablet, enteric-coated**Strength:** 40 mg**Route of Administration:** oral**How Dispensed:**  Rx  OTC**Chemical Name, Molecular Formula, Molecular Weight, Structural Formula****Chemical Name:**

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

**Structure:****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)



Supporting Documents

DMF	SUBJECT	DMF HOLDER	STATUS	REVIEW DATE	LETTER DATE
—	Drug Substance Manufacturer	Byk Gulden	Deficient	4/2/99	2/4/99 4/5/99 10/21/99
—	Supplier	—	Adequate (for tablets)	1/16/98	—
—	High Density Polyethylene (HDPE) Resin	—	Adequate	2/29/97	—
—	Printing Ink Supplier	—	Adequate	4/12/99	—
—	HDPE Bottle Supplier	—	Adequate	9/30/92 (still current)	—
—	HDPE Bottle Supplier	—		Under review (D.Klein)	—
—	HDPE Bottle Supplier	—	Adequate	8/9/99	—
—	Child-Resistant Closure	—	Adequate	4/7/95	—
—	Cap Liner	—	Adequate	4/7/95	—
—	Blister Dome Materials	—	Adequate	2/17/98	—
—	Aluminum Foil Backing (Lidding)	—	Adequate	7/15/97	—
—	Tamper Evident Seal	—	Adequate	3/13/96	—
—	Non child-resistant caps	—	Adequate	8/13/99	—
—	—	—	Adequate (additional information requested)	9/30/99	9/30/99
—	—	—		Under Review (R. Trimmer)	10/1/99

(NOTE: Other than the above packaging DMFs were cited with the original application. However, the applicant was advised that only those that were used in stability studies would be considered for approval. The above list is the revised list submitted in the July 30<sup>th</sup> submission.)

Consults:

Biopharm. Review. See report from David Udo, Ph.D.

Remarks/Comments: See review.

**APPEARS THIS WAY  
ON ORIGINAL**

**Conclusions and Recommendations:** The application is approvable pending resolution of the items listed in the draft deficiency letter.

*/S/*

Marie Kowblansky, PhD  
Review Chemist, HFD-180

11/3/99

*/S/*

Liang Zhou, PhD  
Acting Chemistry Team Leader, HFD-180

11/3/99

cc: Orig. NDA 20-987  
HFD-180/Division File  
HFD-180/LTalarico  
HFD-180/CSO/MWalsh  
HFD-820/JGibbs  
HFD-180/LZhou  
HFD-180/MKowblansky

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**APPEARS THIS WAY  
ON ORIGINAL**

M. Walsh

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS**  
Review of Chemistry, Manufacturing and Controls

**NDA: 20-987**      **Chem. Review: #1**      **Review Date: 6/3/99**  
**Submission Type**      **Document Date**      **CDER Date**      **Assigned Date**  
Original      May 13, 1999      July 7, 1998

JUN - 3 1999

**Name and Address of Applicant:**  
Wyeth Ayerst Laboratories  
P.O. Box 8299  
Philadelphia, PA 19101-8299

**Drug Product Name:**  
Proprietary:      PROTONIX™ Tablets  
Non-proprietary/USAN and CAS:      pantoprazole sodium sesquihydrate  
Code Number (CAS):      138786-67-1  
Code Number (laboratory):      B8610-23 (Byk-Gulden)  
WAY-140951 (Wyeth-Ayerst code)  
Chem. Type/Ther. Class      Type I, New Molecular Entity/Proton Pump Inhibitor

**ANDA Suitability Petition/DESI/Patent Status:** N/A

**Pharmacological Category /Indications:**  
-proton pump inhibitor

**Dosage Form:** Tablet, enteric-coated

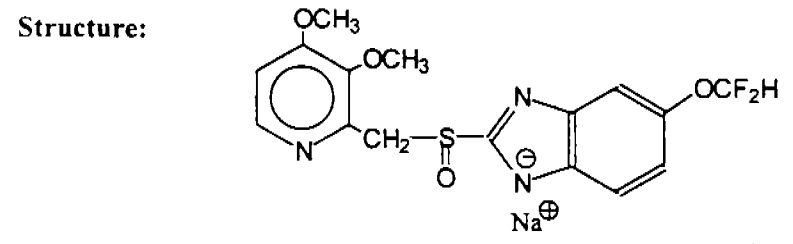
**Strength:** 40 mg

**Route of Administration:** oral

**How Dispensed:**       Rx       OTC

**Chemical Name, Molecular Formula, Molecular Weight , Structural Formula**

**Chemical 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)

**Consults:** None

**Remarks/Comments:** See review.

**Conclusions and Recommendations:** The proposed labeling is unacceptable, as noted in the attached review.

/S/  
Marie Kowblansky, PhD  
Review Chemist, HFD-180

6/3/99

/S/  
Eric P. Duffy, PhD  
Chemistry Team Leader, HFD-180

6/3/99

cc: Orig. NDA 20-987  
HFD-180/Division File  
HFD-180/LTalarico  
DISTRICT OFFICE  
HFD-180/CSO/MWalsh  
HFD-820/JGibbs  
HFD-180/EPDuffy  
HFD-180/MKowblansky

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APPEARS THIS WAY  
ON ORIGINAL

3 PAGE(S) REDACTED

Draft

Labeling

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS**  
Review of Chemistry, Manufacturing and Controls

**NDA: 20-987**                      **Chem. Review: #1**                      **Review Date: 5/3/99**

<b>Submission Type</b>	<b>Document Date</b>	<b>CDER Date</b>	<b>Assigned Date</b>
Original	June 30, 1998 March 29, 1999		July 7, 1998

**Name and Address of Applicant:**

Wyeth Ayerst Laboratories  
P.O. Box 8299  
Philadelphia, PA 19101-8299

**MAY 3 1999**

**Drug Product Name:**

Proprietary:	PROTONIX™ Tablets
Non-proprietary/USAN and CAS:	pantoprazole sodium sesquihydrate
Code Number (CAS):	138786-67-1
Code Number (laboratory):	B8610-23 (Byk-Gulden)
	WAY-140951 (Wyeth-Ayerst code)
Chem. Type/Ther. Class	Proton Pump Inhibitor

**ANDA Suitability Petition/DESI/Patent Status: N/A**

**Pharmacological Category /Indications:**

-proton pump inhibitor

**Dosage Form:** Tablet, enteric-coated

**Strength:** 40 mg

**Route of Administration:** oral

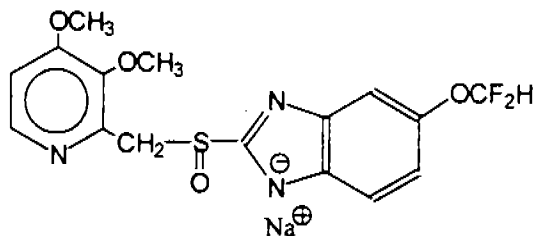
**How Dispensed:**      **R<sub>x</sub>**      **OTC**

**Chemical Name, Molecular Formula, Molecular Weight, Structural Formula**

**Chemical Name :**

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

**Structure:**



**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)

## Supporting Documents

DMF	SUBJECT	DMF HOLDER	STATUS	REVIEW DATE	LETTER DATE
	Drug Substance Manufacturer	Byk Gulden	Deficient	4/2/99	2/4/99 4/5/99
	Supplier		Adequate (for tablets)	1/16/98	----
	High Density Polyethylene (HDPE) Resin		Adequate	2/29/97	----
	Printing Ink Supplier		Adequate	4/12/99	----
	HDPE Bottle Supplier		Adequate	9/30/92 (still current)	----
	HDPE Bottle Supplier		Deficient	3/3/99	3/4/99
	HDPE Bottle Supplier		Waiting for review from	Ravi Harapanhali	
	Child-Resistant Closure		Adequate	4/7/95	----
	Cap Liner		Adequate	4/7/95	----
	Blister Dome Materials		Adequate	2/17/98	----
	Aluminum Foil Backing (Lidding)		Adequate	7/15/97	----
	Tamper Evident Seal		Adequate	9/3/98	----
	Tamper Evident Seal		Adequate	3/13/96	----

(NOTE: Other packaging DMFs were cited in this application. However, only those that pertain to packaging that was actually used in stability studies are considered here.)

## Consults:

Biopharm. Review. See report from David Udo, Ph.D.

## Remarks/Comments

This product is manufactured for Wyeth-Ayerst by Byk-Gulden.

APPEARS THIS WAY  
ON ORIGINAL

**Conclusions and Recommendations**

From the information that has been provided, it is not clear which form of the drug was used in clinical studies, i.e. the sesquihydrate, monohydrate, or any other hydrate. The NDA should be considered not approvable until this issue is resolved.

*/S/*

Marie Kowblansky, PhD  
Review Chemist, HFD-180

*5/3/99*

*/S/*

Eric P. Duffy, PhD  
Chemistry Team Leader, HFD-180

*5/3/99*

cc: Orig. NDA 20-987  
HFD-180/Div. File/ NDA 20-987  
HFD-180/LTalarico  
DISTRICT OFFICE  
HFD-18i/CSO/MWalsh  
HFD-820/JGibbs  
HFD-180/EPDuffy  
HFD-180/Mkowblansky  
R/D init.: EDuffy/5-3-99

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APPEARS THIS WAY  
ON ORIGINAL