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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 209-463
Supporting document/s: 001
Applicant's letter date: June 7, 2016
CDER stamp date: June 7, 2016
Product: Pantoprazole Sodium IV injection
Indication: Gastroesophageal reflux disease (GERD)
Applicant: Exela Pharma Sciences, LLC, Lenoir, NC
Review Division: Division of Gastroenterology and Inborn Errors
Product (DGIEP)
Reviewer: Dinesh Gautam, Ph.D.
Supervisor/Team Leader: Sushanta Chakder, Ph.D.
Division Director: Donna Griebel, M.D.
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Executive Summary

1.1 Recommendations

1.1.1 Approvability

No nonclinical approvability issues have been identified.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The draft labeling of Pantoprazole IV generally conforms to the format specified under 21CFR 201.57(c)(9)(i) through (c)(9)(iii) Requirements for PLLR (Pregnancy and Lactation Labeling Rule) Prescription Drug Labeling. However, the following changes in the proposed label are recommended

8.1 Pregnancy

Sponsor's version:

Risk Summary

(b) (4)

Evaluation: The text should be modified as proposed below.

Risk Summary

Available data from published observational studies did not demonstrate an association of major malformations or other adverse pregnancy outcomes with pantoprazole [see *Data*].

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with pantoprazole. Reproduction studies have been performed in rats at intravenous doses up to 20 mg/kg/day (4 times the recommended human dose) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose) with administration of pantoprazole during organogenesis in pregnant animals and have revealed no evidence of harm to the fetus due to pantoprazole in this study [see *Data*].

A pre- and postnatal development toxicity study in rats with additional endpoints to evaluate the effect on bone development was performed with pantoprazole sodium. Oral doses of 5, 15, and 30 mg/kg/day (approximately 1, 3, and 6 times the exposure on a body surface area basis of a 50kg person dosed at 40 mg/day IV) were administered to pregnant females from gestation day (GD) 6 through lactation day (LD) 21. On postnatal day (PND 4) through PND 21, the pups were administered oral doses at 5, 15, and 30 mg/kg/day (approximately 1, 2.3, and 3.2 times the exposure (AUC) in children aged 6 to 11 years at a dose of 40 mg (6.9 mcg.h/mL)). Changes in bone morphology were observed in pups exposed to pantoprazole *in utero* and through milk during the period of lactation as well as by oral dosing from postnatal day (PND) 4 through PND 21 [see *Use in Specific Populations (8.4)*]. There were no drug-related findings in maternal animals. Advise pregnant women of the potential risk to fetal bone development.

Animal Data

Reproduction studies have been performed in rats at intravenous doses up to 20 mg/kg/day (4 times the recommended human dose based on body surface area) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose based on body surface area) with administration of pantoprazole during organogenesis in pregnant animals and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.

A pre- and postnatal development toxicity study in rats with additional endpoints to evaluate the effect on bone development was performed with pantoprazole sodium. Oral pantoprazole doses of 5, 15, and 30 mg/kg/day (approximately 1, 3, and 6 times the human dose of 40 mg/day on a body surface area basis) were administered to pregnant females from gestation day (GD) 6 through lactation day (LD) 21. On postnatal day (PND 4) through PND 21, the pups were administered oral doses at 5, 15, and 30 mg/kg/day (approximately 1, 2.3, and 3.2 times the exposure (AUC) in children aged 6 to 11 years at a dose of 40 mg (6.9 mcg.h/mL)). There were no drug-related findings in maternal animals. During the preweaning dosing phase (PND 4 to 21) of the pups, there were increased mortality and/or moribundity and decreased body weight and body weight gain at 5 mg/kg/day (approximately equal exposures (AUC) in children receiving the 40 mg dose) and higher doses. On PND 21, decreased mean femur length and weight and changes in femur bone mass and geometry were observed in the offspring at 5 mg/kg/day (approximately equal exposures (AUC) in children at the 40 mg dose) and higher doses. The femur findings included lower total area, bone mineral content and density, periosteal and endosteal circumference, and cross-sectional moment of inertia. There were no microscopic changes in the distal femur, proximal tibia, or stifle joints. Changes in bone parameters were partially reversible following a recovery period, with findings on PND 70 limited to lower femur metaphysis cortical/subcortical bone mineral density in female pups at 5 mg/kg/day (approximately equal exposures (AUC) in children at the 40 mg dose) and higher doses.

Sponsor's version:

8.4 Pediatric Use

Evaluation: The text should be modified as proposed below.

The safety and effectiveness of Pantoprazole Sodium for Injection have not been established in pediatric patients.

Animal Toxicity Data

Adverse effects on bones were observed in a pre- and post-natal developmental toxicity study of pantoprazole at clinically relevant doses. In a pre- and post-natal development study in rats, the pups were administered oral doses of pantoprazole at 5, 15, and 30 mg/kg/day on PND 4 through PND 21, in addition to lactational exposure through milk. On PND 21, decreased mean femur length and weight and changes in femur bone mass and geometry were observed in the offspring at 5 mg/kg/day and higher doses. Changes in bone parameters were partially reversible following a recovery period [see *Use in Specific Populations (8.1)*].

In neonatal/juvenile (rats and dogs) toxicities were similar to those observed in adult animals including gastric alterations, decreases in red cell mass, increases in lipids, enzyme induction and hepatocellular hypertrophy. Increased incidence of eosinophilic chief cells in adult and neonatal/juvenile rats, and atrophy of chief cells in adult rats and in neonatal/juvenile dogs, were observed in the fundic mucosa of stomachs in repeated-dose studies. Full to partial recovery of these effects were noted in animals of both age groups following a recovery period.

13. NONCLINICAL TOXICOLOGY

Sponsor's version:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

A 26-week p53 +/- transgenic mouse carcinogenicity study was not positive.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

There were no effects on fertility or reproductive performance when pantoprazole was given at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area).

Evaluation: No changes are recommended in this section.

Sponsor's version:



Evaluation: Section 13.2 should be deleted.

1.2 Brief Discussion of Nonclinical Findings

PROTONIX[®] IV (pantoprazole sodium) was approved in 2000 (NDA 20-988) for the treatment of gastroesophageal reflux disease (GERD). The current NDA (206-356) is for an IV formulation of pantoprazole sodium submitted under Section 505(b)(2). The proposed formulation of pantoprazole sodium for IV injection differs from the reference listed drug (RLD) with respect to the inactive ingredients. The RLD product, PROTONIX[®] IV contains edetate disodium (b) (4) and sodium hydroxide (pH adjuster). The proposed formulation contains only sodium hydroxide as a pH adjuster and does not contain edetate disodium. The Applicant did not submit any new nonclinical studies of pantoprazole in the NDA. For nonclinical safety, the Applicant relied on the Agency's findings of the safety of the RLD product.

2 Drug Information

2.1 Drug: Pantoprazole sodium IV

2.1.1 CAS Registry Number

102625-70-7

2.1.2 Generic Name

Pantoprazole sodium, USP

2.1.3 Code Name

None

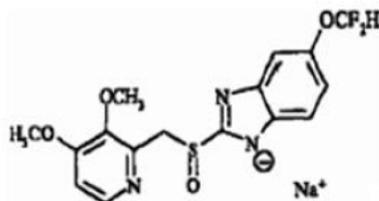
2.1.4 Chemical Name

Benzimidazole, sodium 5-(difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole.

2.1.5 Molecular Formula/Molecular Weight

C₁₆H₁₄F₂N₃NaO₄S (b) (4)

2.1.6 Structure



2.1.7 Pharmacologic class

Proton Pump Inhibitor (PPI).

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA: 20-988: Protonix[®] IV (Pantoprazole): Wyeth Laboratories, Philadelphia, PA; for the treatment of gastroesophageal reflux disease (GERD).

2.3 Clinical Formulation

2.3.1 Drug Formulation

The drug product is supplied as a sterile, unpreserved, single dose, white to off-white lyophilized powder intended for intravenous infusion following reconstitution and subsequent dilution. Each vial contains (b) (4) mg of Pantoprazole Sodium, USP (equivalent to 40 mg Pantoprazole base). The composition of the drug product is shown in the Applicant's Table below.

Component	Quality Standard	Function	Quantity per vial
Pantoprazole Sodium	USP	Drug Substance	(b) (4) 40.0 mg/vial (b) (4)
Sodium Hydroxide	NF	pH adjuster	(b) (4)
(b) (4)	USP	(b) (4)	

2.3.2 Comments on Novel Excipients

No novel excipients were used in the formulation of the drug product.

2.3.3 Comments on Impurities/Degradants of Concern

The Applicant identified nine known impurities. Impurities A, B, C, D, E and F are identified as process related impurities, and impurities (b) (4) are identified as synthesis byproducts. The name, structure, and origin of each impurity are presented in the Applicant's Table below.

Impurity Name	Code Number	Structure	Process/Degradation Impurity	Source / Mechanism
(b) (4)				
(b) (4)				
5-(Difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl)-methyl]sulfonyl]-1 <i>H</i> -benzimidazole	Impurity A		Process Impurity	Impurity A is an (b) (4)
5-(Difluoromethoxy)-2-[[[3,4-dimethoxy-2-pyridinyl)-methyl]thio]-1 <i>H</i> -benzimidazole	Impurity B		Process Impurity	Impurity B is an (b) (4)
5-(Difluoromethoxy)-1 <i>H</i> -benzimidazole-2-thiol	Impurity C		Process Impurity	
Impurity Name	Code Number	Structure	Process/Degradation Impurity	Source / Mechanism
(b) (4)				
5-(difluoromethoxy)-2-[(<i>RS</i>)-[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1-methyl-1 <i>H</i> -benzimidazole	Impurity D		Process Impurity	
A mixture of the stereoisomers of 6,6'-bis(difluoromethoxy)-2,2'-bis[[[3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1 <i>H</i> ,1' <i>H</i> -5,5'-bibenzimidazolyl	Impurity E		Process Impurity	
6-(difluoromethoxy)-2-[(<i>RS</i>)-[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]-1-methyl-1 <i>H</i> -benzimidazole	Impurity F		Process Impurity	

The proposed specifications of these impurities are presented in the Table below (from the Applicant's submission).

Related Compounds	Proposed Specifications	Justification
Impurity A	NMT (b) (4)	(b) (4) ICH Q3B(R2)
Impurity B	NMT	ICH Q3B(R2)
Impurity C	NMT	ICH Q3B(R2)
Impurity D and F	NMT	ICH Q3B(R2)
Impurity E	NMT	ICH Q3B(R2)
Individual Unknown Impurity	NMT	ICH Q3B(R2)
Total Impurities	NMT	ICH Q3B(R2)

The impurities listed in the table above are all qualified at their specification levels according to ICH Q3B(R2) guidance.

No inorganic impurities were detected during the drug development process. The Table below shows the (b) (4) detected in the drug product and all of them are qualified according to ICH (b) (4) guidance.

Solvent	API Supplier Specification	Applicant Specification	ICH Specification
(b) (4)	(b) (4) NMT	(b) (4) NMT	(b) (4) NMT
	NMT	NMT	NMT
	NMT	NMT	NMT
	NMT	NMT	NMT
	NMT	NMT	NMT
	NMT	NMT	NMT

NMT: Not More Than

The Applicant's Table below shows the specification for different impurities and the amount detected in different lots of Pantoprazole Sodium.

TEST	SPECIFICATION	(b) (4)	
		LOT # PS0221112 Results	EXELA LOT #13D023 Results
Description	(b) (4)	(b) (4)	
Identification			
Identification A / USP <197K>		Complies	Passes
Identification B / USP		Complies	Passes
Identification C / Sodium, USP <191>		Positive	Passes
(b) (4)			
Related Compounds by HPLC			
Impurity -A ¹	NMT (b) (4)%	(b) (4) (4)%	(b) (4) 0 (4)%
Impurity -B ¹	NMT (4)%	Not detected	ND

TEST	SPECIFICATION	(b) (4)	
		LOT # PS0221112	EXEIA LOT #13D023
Impurity -C ³	NMT (b) (4)%	Not detected	<(b) (4)%
Impurity -D ³ and F ³	NMT (b) (4)%	(b) (4)%	ND
Impurity -E ³	NMT (b) (4)%	(b) (4)%	ND
Individual Unknown Impurity	NMT (b) (4)%	(b) (4)%	ND
Total impurities	(b) (4) % to (b) (4) %	(b) (4) %	0.1%
Assay / USP	(b) (4) % to (b) (4) % calculated on dried basis.	(b) (4) %	(b) (4) %
(b) (4)	NMT (b) (4) NMT NMT NMT NMT NMT	(b) (4)	(b) (4)
Microbial Limits / USP<61> Total Aerobic Count Yeast and Mold	NMT (b) (4) NMT	Not Tested Not Tested	(b) (4)
Microbial Limits / USP<62> Salmonella Escherichia coli Staphylococcus aureus Pseudomonas aeruginosa	Negative Negative Negative Negative	Not Tested Not Tested Not Tested Not Tested	Negative Negative Negative Negative
Bacterial Endotoxins/ USP<85>	NMT (b) (4) EU/mg	Not Tested	(b) (4) EU/mg

1 - Impurity A is chemically known as 5-(Difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridyl]methyl]sulfonfyl]-1H-benzimidazole.
 2 - Impurity B is chemically known as 5-(Difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridyl]methyl]thio]-1H-benzimidazole.
 3 - Impurity C is chemically known as 5-(Difluoromethoxy)-1H-benzimidazole-2-thiol.
 4 - Impurity D is chemically known as 5-(Difluoromethoxy)-2-[(RS)-(3,4-dimethoxypyridin-2-yl)methyl]sulfanyl]-1-methyl-1H-benzimidazole.

2.4 Proposed Clinical Population and Dosing Regimen

Pantoprazole sodium IV injection is indicated for short-term treatment of gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis. The recommended adult dose is 40 mg once daily by intravenous infusion for 7 to 10 days.

2.5 Regulatory Background

None.

3 Studies Submitted

The Applicant did not submit any nonclinical studies.

3.1 Studies Reviewed

None.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

The applicant did not submit any pharmacology studies of Pantoprazole.

5 Pharmacokinetics/ADME/Toxicokinetics

The applicant did not submit any pharmacokinetic studies with Pantoprazole.

6 General Toxicology

No single- or repeated-dose toxicology study reports were submitted.

7 Genetic Toxicology

No genetic toxicology studies of Pantoprazole were submitted by the Applicant in this NDA.

8 Carcinogenicity

No carcinogenicity studies were submitted.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted.

10 Special Toxicology Studies

No special toxicology studies were submitted.

11 Integrated Summary and Safety Evaluation

Under the current NDA, the applicant is seeking approval of Pantoprazole Sodium IV for the treatment of GERD. The initial approval for PROTONIX[®] IV (pantoprazole sodium) was in 2000 under NDA 20-988.

In this 505 (b)(2) NDA, the applicant did not submit any nonclinical studies and for nonclinical safety, the Applicant relied on the Agency's previous safety assessment of pantoprazole sodium. In the proposed IV formulation of pantoprazole, changes in the inactive ingredients were made as compared to the reference listed drug. The innovator's product contained edetate disodium as a chelating agent [REDACTED] (b) (4) and sodium hydroxide as a pH adjuster. The proposed formulation contains only sodium hydroxide as the pH adjuster, and edetate disodium is omitted. Thus, there are no novel excipients included in the proposed formulation, and there are no safety issues for impurities/degradants in the proposed pantoprazole product. No nonclinical safety issues have been identified for the approval of Pantoprazole sodium IV.

12 Appendix/Attachments: None

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/s/

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03/07/2017

SUSHANTA K CHAKDER
03/07/2017