CENTER FOR DRUG EVALUATION AND RESEARCH

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/BLA REVIEW AND EVALUATION

Application number:	217512
Supporting document/s:	1
Applicant's letter date:	8/17/2023
CDER stamp date:	8/17/2023
Product:	Pantoprazole sodium injection
Indication:	Gastroesophageal reflux disease (GERD) associated with a history of Erosive Esophagitis (EE) Pathological hypersecretion conditions including Zollinger-Ellison (ZE) Syndrome
Applicant:	Baxter Healthcare Corporation
Review Division:	Division of Gastroenterology (DG)
Reviewer:	Achinto Saha, Ph.D.
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1 Executive Summary

1.2 Brief Discussion of Nonclinical Findings

In this 505 (b)(2) NDA, the applicant is relying on the Agency's previous findings of safety and efficacy for the listed drug, Protonix IV (NDA 020988; Wyeth Pharmaceuticals LLC). Pantoprazole, a substituted benzimidazole, is a proton pump inhibitor that blocks the final step of gastric acid production. Pantoprazole inhibits the gastric acid production by covalently binding to the hydrogen potassium ATPase (H+, K+-ATPase) enzyme system at the secretory surface of the gastric parietal cell. The binding of pantoprazole sodium with H+, K+-ATPase leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The nonclinical safety of pantoprazole sodium has been established in pharmacology, pharmacokinetics, general toxicology, genotoxicity, reproductive toxicity, and carcinogenicity studies conducted in support of the original NDA for Protonix, the listed drug. Pantoprazole sodium was positive in the *in vitro* human lymphocyte chromosomal aberration assay, in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay and in one of two mouse micronucleus tests for clastogenic effects. Pantoprazole sodium was negative in the *in vitro* Ames test, 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. In 2-year carcinogenicity studies, neoplastic changes were observed in several organs including malignant neuroendocrine cell tumors and adenocarcinomas of the gastric fundus, malignant squamous cell carcinomas of forestomach, adenocarcinoma of the duodenum, hepatocellular adenomas and carcinomas and thyroid follicular cell adenomas and carcinomas, which are included in the existing labeling for Protonix IV. Pantoprazole had no effects on female or male fertility in rats and did not show any evidence of impaired fertility or harm to the fetus in embryofetal development studies in rats or rabbits. However, in a pre- and post-natal developmental study in rats, pantoprazole sodium produced changes in bone morphology which included decreased mean femur length and weight and changes in femur bone mass and geometry.

Although, the active ingredient of the Pantoprazole Sodium in 0.9% Sodium Chloride for injection is same as the listed drug, it has two additional excipients, the (b) (4) histidine and the pH adjusting agent, hydrochloric acid. The excipients used in the proposed formulation have been widely used in approved intravenous drug products. The safety of the levels of histidine is justified by its presence in other FDA approved drug products at levels up to 18-fold higher than the level in the proposed Pantoprazole Sodium in 0.9% Sodium Chloride for injection formulation.

The impurity levels for both the drug substance (pantoprazole sodium) and drug product are controlled as per ICH Q3A and ICH Q3B(R2). The levels of all the impurities except pantoprazole related compound C were within the identification and qualification threshold limits of (b) (4) %. To justify the higher levels of Compound C impurity in the drug

product, the Applicant performed a 14-day intravenous repeated dose general toxicity study which also included an *in vivo* bone marrow micronucleus assay. The results showed that pantoprazole related compound C at (b) (4) mg/kg/day and (b) (4) mg/kg/day (which corresponds to (b) (4)% and (b) (4)% qualification limit, respectively, based on the maximum human dose of pantoprazole sodium for Injection) was negative for micronucleus assay and did not produce any adverse effects in rats. The residual solvents are controlled as per ICH Q3C Guidance, and there are no safety concerns for residual solvents in the drug product. Toxicological assessment of the leachables from the primary packaging of the drug product did not reveal a safety concern for the leachables from the container/closure system.

1.3 Recommendations

1.3.1 Approvability

No nonclinical approvability issues have been identified for NDA 217512 from the pharmacology/toxicology standpoint.

1.3.2 Additional Non-Clinical Recommendations

None

1.3.3 Labeling

For the nonclinical sections of labeling, the Applicant adopted the approved labeling for Protonix IV Injection. The proposed language for the nonclinical sections (Sections 8 and 13) of the labeling is acceptable.

2 Drug Information

2.1 Drug: Pantoprazole sodium in 0.9% sodium chloride injection

CAS Registry Number (Optional): 164579-32-2

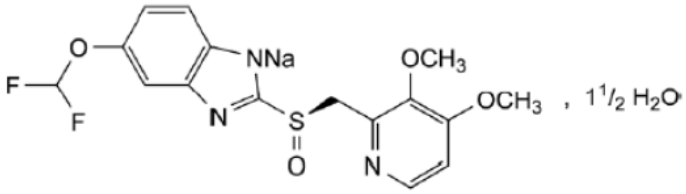
Generic Name: Pantoprazole Sodium

Code Name: N/A

Chemical Name: 5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

Molecular Formula/Molecular Weight: $C_{16}H_{14}F_2N_3NaO_4S \bullet 1½\ H_2O$/ 432.4

Structure or Biochemical Description



Pharmacologic Class: Proton pump inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 156870, NDA 020998, DMF (b) (4) and DMF (b) (4)

2.3 Drug Formulation

The proposed product is a premix ready-to-use formulation in three different presentations (40 mg/100 mL, 40 mg/50 mL and 80 mg/100 mL) compared to the LD, which is supplied as 40 mg lyophilized powder in a single-dose vial for reconstitution.

2.4 Comments on Novel Excipients

Pantoprazole Sodium in 0.9% Sodium Chloride for Injection has the same active ingredient as the listed drug (Protonix IV). However, it has two additional excipients, the (b) (4) histidine and the pH adjusting agent, hydrochloric acid. The excipients used in the proposed formulation are present in approved intravenous drug products. The levels of all the excipients used in Pantoprazole Sodium in 0.9% Sodium Chloride for Injection are within the levels present in approved intravenous products listed in the FDA inactive ingredient database (IID), except histidine, which is higher than the IID levels, as shown in the Table below from the Applicant's submission.

Table 1. Comparison of Inactive Ingredient Levels in Pantoprazole Sodium in 0.9% Sodium Chloride Injection versus the IID

Inactive Ingredient / Excipient	Excipient Amount in Pantoprazole Sodium in 0.9% Sodium Chloride Injection	Excipient Amount per 100 mL	Maximum Daily Intake (MDI) of Inactive Ingredient[a]	Maximum Daily Exposure (MDE) based on IID Levels for Intravenous Route of Administration[b]	MDI ≤ IID MDE
Sodium Chloride	9 mg/mL	900 mg	2700 mg	28773 mg (UNII 451W47IQ8X)	Yes
Edetate Disodium	0.02 mg/mL	2 mg	6 mg	19 mg (UNII 7FLD91C86K)	Yes
Histidine	1.55 mg/mL	155 mg	465 mg	63 mg (UNII 4QD397987E)	No
Sodium Hydroxide	As required to adjust pH	As required to adjust pH	N/A	Max. Potency per unit dose = 2.83%w/v (UNII 55X04QC32I)	Yes
Hydrochloric Acid	As required to adjust pH	As required to adjust pH	N/A	Max. Potency per unit dose = 0.7%w/v (UNII QTT17582CB)	Yes

MDI = Maximum Daily Intake; IID = Inactive Ingredient Database; USP = United States Pharmacopeia; NF = National Formulary

[a] Maximum daily intake is based on a maximum daily dose of pantoprazole of 240 mg/day for an adult patient. Based on dosing and administration, three 80 mg doses would be used to deliver this dose, therefore 300 mL represents the maximum daily volume to be administered.

[b] http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

The safety of the levels of histidine in the proposed product is justified by its presence in other FDA approved drug products (in parenteral nutrition products) at levels up to 18-fold higher than that at the maximum dose of the proposed pantoprazole sodium Injection as shown in the Table below (from the Applicant's submission)

Table 2. Maximum Daily Intake (MDI) of Histidine from Pantoprazole Sodium in 0.9% Sodium Chloride Injection Compared to CDER Approved Products

Product Name/Strength	Histidine Concentration	Maximum Infusion Volume	MDI of Histidine
Pantoprazole Sodium in 0.9% Sodium Chloride Injection	1.55 mg/mL	300 mL/day[a]	465 mg
Aminosyn II 10%	4.5 mg/mL	1400 mL/day[b]	6300 mg
FreAmine III 10%	2.8 mg/mL	1400 mL/day[b]	3920 mg
Prosol 20%	11.8 mg/mL	700 mL/day[b]	8260 mg
Travasol 10%	4.8 mg/mL	1400 mL/day[b]	6720 mg

[a] Based on a maximum daily dose of pantoprazole of 240 mg/day for an adult patient.

[b] Protein requirement in stable adult patients is 0.8-1.0 g/kg/day and 1.5-2.0 g/kg/day in critically ill patients. Assuming the maximum dose of 2.0 g/kg/day in an average adult 70 kg patient, protein requirement would be 140 g. To deliver this dose, 1400 mL of 10% solution and 700 mL of 20% solution would be required.

2.5 Comments on Impurities/Degradants of Concern

The drug related substances in the premix Pantoprazole Sodium in 0.9% Sodium Chloride for Injection increased with room light exposure as shown in the Applicant's Table below. However, related compound C was the only substance observed above the ICH qualification threshold of (b) (4)% when exposed to room light. To qualify compound C at the proposed limits of up to (b) (4)% in the proposed product as per ICH Q3B (R2), the Applicant conducted a 14- day intravenous infusion repeated-dose general toxicity study in rats, which also included an *in vivo* bone marrow micronucleus assay. The key study findings include.

- No compound C-related adverse effects were observed in animals following 14-day repeated dosing.
- Compound C did not induce micronucleated polychromatic erythrocytes in rats bone marrow and is considered nonclastogenic under the conditions of the study.

Table 3. Comparison of Highest Related Substances Observed in the Drug Product vs. the LD (Protonix I.V.)

Related Substance	Largest Mean Value (%) Observed in Developmental Units (40 mg/ 100 mL), Exposed to Room Light for 72 Hours[a]	Largest Value (%) Observed in Registration Stability Units (40 mg/ 50 mL[b]), 72 Hours at Room Temperature after 8 Months at -20 °C	Largest Mean Value (%) Observed in Protonix I.V. After Dilution at Expiry[f]
Related Compound C	(b) (4)		
Related Compound A			
Related Compound D/F			
Related Compound E			
Related Compound B			
Unknown (b) (4)			
Unknown			
Unknown			
Unknown			
Unknown			
Unknown			
Unknown			
Unknown			
(b) (4)			
Unknown (b) (4)			
Unknown			
Unknown			

Table 3. Comparison of Highest Related Substances Observed in the Drug Product vs. the LD (Protonix I.V.)

Related Substance	Largest Mean Value (%) Observed in Developmental Units (40 mg/ 100 mL), Exposed to Room Light for 72 Hours[a]	Largest Value (%) Observed in Registration Stability Units (40 mg/ 50 mL[b]), 72 Hours at Room Temperature after 8 Months at -20 °C	Largest Mean Value (%) Observed in Protonix I.V. After Dilution at Expiry[f]
(b) (4)			
Total Related Substances			

[a] Developmental study BXU571327: Photostability of Pantoprazole Sodium in 0.9% Sodium Chloride Injection in Galaxy PL2040 Containers.
[b] Stability Study 2022043 (Batch 573772 1).
[c] Protonix lot 488975, diluted to 40 mg/100 mL, 24 hours at room temperature.
[d] Protonix lot 488975, diluted to 80 mg/100 mL, time zero at room temperature.
[e] Protonix lot 487400, diluted to 40 mg/50 mL time zero at room temperature.
[f] Study BXU562583: Assessment of Pantoprazole Sodium Marketed Products.
[g] Protonix lot 488975, diluted to 80 mg/ 100 mL, 24 hours at room temperature

Residual Solvents

The (b) (4) present in the drug substance and drug product are controlled at or below USP/ ICH Q3C limits, and there are no safety concerns.

Container Closure system:

Pantoprazole Sodium in 0.9% Sodium Chloride Injection is packaged in a single-port PL 2040 plastic GALAXY container-closure system which has been used for decades for several FDA approved aqueous IV products. The GALAXY container-closure system consists of PL 2040 (b) (4) The PL 2040 (b) (4) (b) (4) (b) (4) (b) (4)

Extractables

An extraction study was conducted to evaluate the extractables from the primary packaging (Galaxy PL2040 container) of the drug product with (b) (4) (b) (4) (b) (4)

50 mL Galaxy PL2040 containers were filled with either pH 3 or pH 10 aqueous solvent systems and the filled bags were frozen (-20°C for 1 week), thawed, then stored at 5°C

or 25°C for 30 days. Extracts were analyzed by Headspace Gas Chromatography / Mass Spectrometry methods. The Table below shows a total of 55 compounds that were detected in the aqueous extracts (pH 3 & pH 10) of the PL2040 Galaxy packaging system above the method reporting limits. Most of the compounds identified in the extractable study with the Galaxy packaging system that are likely to be detected in the leachable study are a variety of (b) (4) originating from (b) (4) the (b) (4) Thus, it was assumed that the hydrolysis products (b) (4) (b) (4) will be the most prominent leachables detected.

Table 4. Extractable Profile of Galaxy PL2040

ID	ORGANIC COMPOUND	CAS No. / ToxID	µg/L
IC	(b) (4)		
IC			
TIC			
IC			
TIC			
IC			
IC			
TIC			
MPC			
MPC			
IC			
IC			
MPC			
IC			
MPC			
TIC			
IC			
IC			
IC			
TIC			
MPC			

TIC	(b) (4)
IC	
TIC	
IC	
IC	
IC	
MPC	
MPC	
TIC	
TIC	
IC	
IC	
IC	
MPC	
TIC	
IC	
IC	
TIC	

IC: Identified Compound, MPC: Most Probable Compound, TIC: Tentatively Identified Compound,

Leachables

A leachable study was performed to evaluate the leachable profile of non-volatile, semi-volatile, and volatile organic compounds. The 40 mg/50 mL and 40mg/100 mL samples were stored for 8 months at -20 ˚C followed by 21 days at 5 ˚C or 2 days at 25 ˚C and the 80 mg/100 mL samples were stored for 15 months at -20 ˚C followed by 21 days at 5 ˚C or 2 days at 25 ˚C. Samples stored under each condition were analyzed via HRAM-UPLC/MS, GC/MS, and HS-GC/MS with a reporting limit of lower than (b) (4) ug/L which corresponds to an exposure of (b) (4) µg/day. The Table below shows the summary of all leachables detected and their respective concentrations observed above the Analytical Evaluation Threshold (AET) level.

Table 5. Leachable Profile of Pantoprazole Sodium in 0.9% Sodium Chloride Injection (40 mg/50 mL) Exhibit Batches (8 Months at -20°C)

Leachables ≥AET	CAS No.	Concentration (µg/L)	
		(b) (4)	
		21 days at 5°C	2 days at 25°C
(b) (4)			

Table 6. Leachable Profile of Pantoprazole Sodium in 0.9% Sodium Chloride Injection (40 mg/100 mL) Exhibit Batches (8 Months at -20°C)

Leachables ≥AET	CAS No.	Concentration (µg/L)	
		(b) (4)	
		21 days at 5°C	2 days at 25°C
(b) (4)			

Table 7. Leachable Profile of Pantoprazole Sodium in 0.9% Sodium Chloride Injection (80 mg/100 mL) PE Batch (15 Months at -20°C)

Leachables ≥AET	CAS No.	Concentration (µg/L)	
		(b) (4)	
		21 days at 5°C	2 days at 25°C
(b) (4)			

A toxicological risk assessment of leachables from the primary packaging of the drug product was performed and all leachables at exposure levels (b) (4) µg/day were assessed, as per the Product Quality Research Institute's (PQRI) Parental and Ophthalmic Drug Product (PODP) Working Group for Leachables and Extractables. The following Table shows the amounts of leachables that a patient would be exposed per day from Pantoprazole Sodium in 0.9% Sodium Chloride Injection with a maximum daily dose of 300 mL (240 mg maximum daily dose÷ 80 mg/100 mL= 300 mL). The tolerable intake (TI) and Permissible Daily Exposures (PDE) were calculated in accordance with ISO 10993-17 and ICH Q3C(R8), respectively.

Table 8. Worst-Case Daily Exposure to Leachables Identified in Pantoprazole Sodium Premix

Leachable	CAS No.	Maximum Concentration (µg/L)	Maximum Total Concentration (µg/L)	Maximum Exposure[1] (µg/day)	Tolerable Intake/PDE[2] (µg/day)	Margin of Safety[3]
(b) (4)						

[1]Maximum Daily Exposure = Maximum Total Concentration (µg/L) x Maximum Daily Volume of Pantoprazole Sodium Premix (L/day); Example: (b) (4) = (b) (4) µg/L× (b) (4) L/day = (b) (4) µg/day

[2]Assumes a conservative adult body weight of 50 kg.

[3]Margin of Safety (rounded to nearest whole number) =Tolerable Intake (µg/day) ÷ Maximum Daily Exposure (µg/day); Example: (b) (4) = (b) (4) µg/day ÷ (b) (4) µg/day = (b) (4)

As shown in the Table above, the estimated maximum uptake of all the leachable were less than the PDE and there are no safety concerns.

2.6 Proposed Clinical Population and Dosing Regimen

Pantoprazole Sodium in 0.9% Sodium Chloride Injection is indicated for short-term treatment (7 to 10 days) of adult patients with

- gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis (EE) with the recommended dosage of 40 mg/day by intravenous infusion.

- pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome and the recommended dose is 80 mg intravenously every 12 hours which can be adjusted to 80 mg intravenously every 8 hours.

2.7 Regulatory Background: N/A

3 Studies Submitted

3.1 Studies Reviewed

- Pantoprazole related compound C: 14-day intravenous infusion toxicity study with evaluation of induction of micronucleated erythrocytes in bone marrow in Sprague Dawley rats (Study # U-22041).
- Determination of extractable chemical compounds migrating from Galaxy PL 2040 bag system used for the storage of different drug products (Study report # TE212955, TE212956, TE212957).
- Determination of leachable chemical compounds, migrating from a Galaxy PL2040 bag system after contact with pantoprazole sodium in 0.9% Nacl solution (Study report # TE230128, TE230129).
- Toxicological risk assessment of leachables associated with pantoprazole sodium premix in a Galaxy PL2040 bag system (Study # BXU594282)

6 General Toxicology

Study title: Pantoprazole related compound C: 14-Day Intravenous Infusion Toxicity Study with Evaluation of Induction of Micronucleated Erythrocytes in Bone Marrow in Sprague Dawley Rats

Study no.:	U-22041
Study report location:	4.2.3.7.6
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 8, 2022
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Pantoprazole related compound C, (b) (4), purity 98.5%

Key Study Findings

No test article (compound C)-related adverse effects were observed in the 14-day intraven epeated dose toxicity study in rats. The NOAEL was the highest tested dose of (b) (4) mg/kg/day.

Methods

Doses:	(b) (4) and (b) (4) mg/kg/day
Frequency of dosing:	Once daily for 14 days
Route of administration:	Intravenous infusion
Dose volume:	10 mL/kg
Formulation/Vehicle:	Solution/Normal saline (0.9% sodium chloride w/v) pH 10.7 ± 0.1
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	10/sex/group
Age:	8 - 9 weeks old
Satellite groups:	None
Unique study design:	N/A
Deviation from study protocol:	None

Observations and Results

Mortality

There were no treatment-related mortalities at any dose level. All animals survived to their scheduled necropsy.

Clinical Signs

Clinical signs were monitored once daily, and no test article related clinical signs were observed at any dose level.

Body Weights

Individual body weights were measured twice per week during the dosing period. No test article-related changes on body weights were observed in either sex at any dose level.

Feed Consumption

Feed consumption was measured once weekly during the dosing period. No test article-related changes in food consumptions were observed.

Ophthalmoscopy

Ophthalmoscopic examinations were conducted in all animals once during pre-dose and once on Day 13 of the dosing period. No treatment-related effects on ophthalmic parameters were observed.

Hematology

Blood samples were collected from all surviving animals on Day 15 for hematology examination. No test article-related changes in hematology parameters were observed at any dose level.

Clinical Chemistry

Slightly increased alanine aminotransferase (24% and 19% in males and 20% and 15% in females at (b) (4) and (b) (4) mg/kg/day, respectively, vs. control group) and aspartate aminotransferase (16% and 11% in males and 11% and 15% in females at (b) (4) and

(b) (4) mg/kg/day, respectively, vs. control group) were observed without any histopathological findings in the related organs.

Coagulation
No test article-related changes in coagulation parameters were observed at any dose level.

Urinalysis
Urine was collected on Day 15 of the dosing period. There were no treatment related changes on urinalysis.

Gross Pathology
Gross pathology examinations were conducted at necropsy. No treatment-related adverse macroscopic findings were observed.

Organ Weights
The weights of the following organs were measured at the time of necropsy: adrenal gland, brain, epididymis, heart, kidney, liver, lung, ovary, pituitary gland, prostate, seminal vesicle, spleen, testes, thymus, thyroid and parathyroid glands, and uterus. No treatment-related adverse effects on organ weights were observed.

Histopathology
Adequate Battery: Yes, study report pages 32-34.
Peer Review: Yes
Histopathology Findings: No treatment related histopathological findings were observed.

Special Evaluation
None

Toxicokinetics
Not performed

Dosing Solution Analysis
All formulations met the acceptance criteria (mean content: (b) (4) to (b) (4) %, relative standard deviation: ± (b) (4) %) and were within (b) (4) % of the mean target concentrations (means ranging from (b) (4) to (b) (4) % of nominal).

7 Genetic Toxicology

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

The micronucleus assay with pantoprazole related compound C was performed as part of the 14-day intravenous repeated dose toxicity study in rats. The bone marrow erythrocyte samples were collected during necropsy at the end of the 14-day toxicity study.

Key Study Findings

The test article (compound C) did not induce micronucleated polychromatic erythrocytes in rats bone marrow and is considered nonclastogenic under the conditions of the study.

Methods	
Doses in definitive study:	(b) (4) and (b) (4) mg/kg/day
Frequency of dosing:	Once daily for 14 days
Route of administration:	Intravenous infusion
Dose volume:	10 mL/kg
Formulation/Vehicle:	Solution/Normal saline (0.9% sodium chloride w/v) pH 10.7 ± 0.1
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	5/sex/group
Satellite groups:	None
Basis of dose selection:	The doses of (b) (4) and (b) (4) mg/kg/day were selected based on the maximum daily dose of Pantoprazole (240 mg/day) and the desired limit of qualification of Pantoprazole related compound C (b) (4) and (b) (4)%) in the finished product ((b) (4) mg/day × (b) (4) = (b) (4) mg/day÷ (b) (4) kg = (b) (4) mg/kg/day human do which corresponds to (b) (4) x (b) (4) (conversion factor for rat)= (b) (4) mg/kg/day in rats for (b) (4) qualification limit and (b) (4) (b) (4) (b) (4) mg/kg/day for (b) (4)% qualification limit.
Negative control:	Normal saline (0.9% sodium chloride w/v) pH 10.7 ± 0.1
Positive control:	Cyclophosphamide (b) (4) mg/kg/day)

Study Validity

Study met the criteria for a valid assay. The incidences of micronucleated polychromatic erythrocytes (MNPCEs) in the vehicle control group were within the range of the historical control data in the testing facility [males (0 to 0.067%) and females (0 to 0.068%)]. A significant increase in the incidence of MNPCEs was observed in the positive control group.

Results

The mean values of the percentage of micronucleated polychromatic erythrocytes (%MNPCEs) were 0.065%, 0.065% and 0.07% in males and 0.065% 0.065% and 0.069% in females at doses of (b) (4) and (b) (4) mg/kg, respectively. Thus, IV administration of Pantoprazole related compound C to SD rats for 14 consecutive days had no significant increase in the micronucleus frequency of rat bone marrow cells under the conditions of the study. The results are shown in the Applicant's Table below.

Table 9: PCE and MNPCE frequencies following treatment with Pantoprazole related compound C

Treatment	Dose mg/kg	Male		Female	
		%PCEs	MNPCEs (%)	%PCEs	MNPCEs (%)
Vehicle Control	(b) (4)	50	0.065	50	0.065
Pantoprazole related compound C		49	0.065	50	0.065
		51	0.07	51	0.069
Positive control (CP)		51	0.54	51	0.53

Values are expressed as mean of 5 animals; %PCEs =Polychromatic Erythrocytes/ Total Erythrocytes x100; MNPCEs = Micronucleated PCEs; CP=Cyclophosphamide monohydrate; *Table created by reviewer, from Applicant's raw data*

11 Integrated Summary and Safety Evaluation

Pantoprazole Sodium (Protonix IV) is currently approved for the short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis (EE) and pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome. In this 505 (b)(2) NDA, the Applicant is relying on the Agency's previous findings of safety and efficacy for the listed drug, Protonix IV (NDA 020988; Wyeth Pharmaceuticals LLC).

Comprehensive nonclinical pharmacology, pharmacokinetics, general toxicology, genotoxicity, reproductive toxicity, and carcinogenicity studies of pantoprazole sodium were conducted in support of the original NDA for the listed drug, Protonix IV. Pantoprazole is a proton pump inhibitor that blocks the final step of gastric acid production. Pantoprazole inhibits the gastric acid production by covalently binding to the hydrogen potassium ATPase (H+, K+-ATPase) enzyme system at the secretory surface of the gastric parietal cell. The binding of pantoprazole sodium with H+, K+-ATPase leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The nonclinical safety of pantoprazole sodium has been established in nonclinical studies conducted for the approval of the listed drug.

Pantoprazole sodium was positive in the *in vitro* human lymphocyte chromosomal aberration assay, in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay and in one of two mouse micronucleus tests for clastogenic effects. Pantoprazole sodium was negative in the *in vitro* Ames test, 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. In 2-year carcinogenicity studies, neoplastic changes were observed in several organs which are included in the existing labeling for Protonix IV. Pantoprazole had no effects on female or male fertility in rats and did not show any evidence of impaired fertility or harm to the fetus in rats or rabbits. However, in a pre- and postnatal developmental study in rats, changes in bone morphology (decreased mean femur length and weight and changes in femur bone mass and geometry) 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.

Although, the active ingredient of the proposed formulation, Pantoprazole Sodium in 0.9% Sodium Chloride for injection is same as the listed drug, it has two additional excipients, the (b) (4) histidine and the pH adjusting agent, hydrochloric acid. The excipients used in the proposed formulation is present in approved intravenous drug products. However, the level of histidine in the proposed formulation is higher than that present as an excipient in approved drug products. The safety of the levels of histidine is justified by its presence in other FDA approved drug products (in parenteral nutrition products) at levels up to 18-fold higher than the level in the proposed Pantoprazole Sodium injection formulation.

The impurity levels for both the drug substance and drug product are controlled as per ICH Q3A and ICH Q3B(R2), respectively. The levels of all the impurities except pantoprazole related compound C were within the qualification threshold of (b) (4) %. The Applicant performed a 14-day intravenous repeated dose impurity qualification general toxicity study of compound C in rats, which also included an *in vivo* bone marrow micronucleus assay. Compound C at (b) (4) mg/kg/day and (b) (4) mg/kg/day was negative in the micronucleus assay and did not produce any treatment related adverse effects in rats. The residual solvents are controlled as per ICH Q3C Guidance, and there are no safety concerns for the residual solvents in the drug product.

Pantoprazole Sodium in 0.9% Sodium Chloride Injection is packaged in single-port PL 2040 plastic GALAXY container-closure system consisting of PL 2040 (b) (4)

Extractable and leachable studies were conducted for safety assessment of the potential leachables from the container closure system. A toxicological safety assessment of the leachables from the primary packaging of the drug product did not identify any safety concerns.

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/s/

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