CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217512Orig1s000

SUMMARY REVIEW

CDTL/Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Irena Lavine, MD Cross-Disciplinary Team Leader Joyce Korvick, MD, MPH Deputy Director for Safety Division of Gastroenterology OII/OND/CDER/FDA
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	NDA 217512
Applicant	Baxter Healthcare Corporation
Date of Submission	August 17, 2023
Anticipated Action Date	February 14, 2024
PDUFA Goal Date	June 17, 2024
Proprietary Name	None
Established or Proper Name	Pantoprazole Sodium in 0.9% Sodium Chloride Injection
Dosage Form(s)	Injection Strengths: • 40 mg/100 mL (0.4 mg/mL) pantoprazole in single-dose flexible container • 40 mg/50 mL (0.8 mg/mL) pantoprazole in single-dose flexible container • 80 mg/100 mL (0.8 mg/mL) pantoprazole in single-dose flexible container
Applicant Proposed Indication(s)/Population(s)	1) For the short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE). Safety and efficacy as a treatment of patients with GERD and a history of EE for more than 10 days have not been demonstrated. 2) For the treatment of pathological hypersecretion conditions including Zollinger-Ellison (ZE) Syndrome in adults.
Action or Recommended Action:	Approval
Approved/Recommended Indication(s)/Population(s) (if applicable)	Same as Applicant Proposed Indication(s)/Population(s)

Disciplines Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer	Irena Lavine
CDTL	Irena Lavine
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Project Manager	Kristina Luong
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Clinical Pharmacology	N/A
Statistics	N/A
DG Safety	Joyce Korvick, Jackie Lee Hoffman (Safety RPM)
ADL	Joette Meyer
OPQ/ATL	Hamid Shafei
OPQ/Drug Product	Caroline Strasinger, Hamid Shafei
OPQ/Drug Substance	Friedrich Burnett, Larry Perez, Donna Christner
OPQ/Process, Facilities	Dacie Bridge, Yan Zheng
OPQ/Microbiology	Catherine Gilbert, Yan Zheng
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OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Benefit-Risk Assessment

The Applicant, Baxter Healthcare Corporation, submitted NDA 217512 for Pantoprazole Sodium in 0.9% Sodium Chloride Injection under the 505(b)(2) pathway on August 17, 2023. This NDA relies on the findings of safety and effectiveness for the listed drug (LD), Protonix I.V. (pantoprazole sodium) for injection (NDA 020988) from Wyeth Pharmaceuticals LLC (a subsidiary of Pfizer) approved March 22, 2001. Protonix I.V. is a proton pump inhibitor (PPI) indicated in adults for the following:

- Short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis (EE).
- Pathological hypersecretion conditions including Zollinger-Ellison (ZE) Syndrome.

The Applicant is requesting the same indications as approved in the LD labeling.

This application provides for a new dosage form. The LD is supplied as a freeze-dried powder in a single-dose vial containing 40 mg pantoprazole that requires reconstitution with 10 mL of 0.9% sodium chloride and further dilution with 5% dextrose, 0.9% sodium chloride, or lactated ringers to concentrations of 40 mg/100 mL (0.4 mg/mL) or 80 mg/100 mL (0.8 mg/mL). As a ready-to-use, frozen, premixed solution, the proposed Pantoprazole Sodium in 0.9% Sodium Chloride Injection (supplied in 3 strengths 40 mg/100 mL, 40 mg/50 mL, and 80 mg/100 mL pantoprazole) does not require reconstitution or dilution prior to intravenous administration. The formulations for the proposed product represent commonly used dilutions of pantoprazole which are similar to the LD following reconstitution and dilution, and provide another option for administering pantoprazole intravenously which may be easier to prepare and administer compared to the LD.

Although the proposed product provides the equivalent amount of active ingredient pantoprazole as found in the LD following reconstitution and dilution, the proposed product has two additional excipients, histidine which is used as a (b) (4) and hydrochloric acid which is used as a pH adjustor. Histidine is listed on the FDA Inactive Ingredient Database (IID) as a component of formulations administered intravenously. Histidine is also routinely delivered intravenously as part of the amino acid component of parenteral nutrition. The maximum daily intake (MDI) of histidine in the proposed product exceeds the maximum daily exposure (MDE) based on IID levels for intravenous administration. However, 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. As such, its presence in the formulation will not impact the safety of pantoprazole for the intended indications. Further, differences in the pH adjustor hydrochloric acid (also commonly used in many pharmaceutical products) are not expected to impact the in vivo performance of pantoprazole.

In summary, given the compositional similarity, physicochemical comparability, similarities in the clinical use for administration as an intravenous infusion, and recognizing the linear pharmacokinetics of pantoprazole as demonstrated in the clinical literature and by the Prescribing Information, the Applicant's scientific bridge between the LD and the proposed drug product is established from the biopharmaceutics perspective.

No clinical biopharmaceutical, pharmacologic, efficacy, or safety studies have been performed for Pantoprazole Sodium in 0.9 % Sodium Chloride Injection by the Applicant. The active moiety was first approved as oral tablets on February 20, 2000. There are additional approved drug products containing the active moiety (i.e., NDA 020987 PROTONIX (pantoprazole sodium) delayed-release tablets, NDA 022020 PROTONIX (pantoprazole sodium) for delayed-release oral suspension, NDA 209463 Pantoprazole sodium for injection). Therefore, there is clinical experience with the use of pantoprazole over the last several decades. To support the registration of Pantoprazole Sodium in 0.9% Sodium Chloride Injection, the Applicant conducted a literature search, and there were no new concerning safety findings of pantoprazole identified.

The following benefit-risk assessment is based upon review of the Applicant's NDA 217512 submission on August 17, 2023. No deficiencies were identified, and the application is recommended for approval by all disciplines for adults with the following indications:

- Short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis (EE).
- Pathological hypersecretion conditions including Zollinger-Ellison (ZE) Syndrome.

Designated Signatory Authority Comments

This 505(b)(2) submission for NDA 217512 for Pantoprazole Sodium in 0.9% Sodium Chloride Injection provides for a ready-to-use, frozen, premixed solution. The proposed Pantoprazole Sodium in 0.9% Sodium Chloride Injection (supplied in 3 strengths 40 mg/100 mL, 40 mg/50 mL, and 80 mg/100 mL pantoprazole) does not require reconstitution or dilution prior to intravenous administration. The application proposes the same adult indications listed in the LD (NDA 020988) which is currently marketed. As noted, there are no clinical studies performed for this submission, and the scientific bridge provided was found to be acceptable. The risk-benefit of this product appears to be the similar to that of the LD, with the advantage of being pre-mixed. I agree with the review outlined here that recommends this product for approval.

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

The Applicant, Baxter Healthcare Corporation, submitted new drug application (NDA) 217512 for Pantoprazole Sodium in 0.9% Sodium Chloride Injection under the 505(b)(2) pathway relying on the findings of safety and effectiveness for the listed drug (LD), Protonix I.V. (pantoprazole sodium) for injection (NDA 020988), approved March 22, 2001. Protonix I.V. is a proton pump inhibitor (PPI) indicated in adults for the following:

- Short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis (EE).
- Pathological hypersecretion conditions including Zollinger-Ellison (ZE) Syndrome.

For GERD associated with EE, intravenous administration of pantoprazole sodium is intended for patients who cannot receive treatment with oral pantoprazole sodium delayed-release tablets or oral suspension. The Applicant is requesting the same indications as approved in the LD labeling.

Gastroesophageal reflux disease (GERD) is a condition in which the reflux of gastric contents into the esophagus results in symptoms and/or complications.[1] Common symptoms of GERD include heartburn and regurgitation. Other symptoms of GERD may include chest pain, nausea, dysphagia, odynophagia, chronic cough, and hoarseness.[2] GERD can present as non-erosive reflux disease or erosive esophagitis. GERD is associated with an increased risk of esophagitis, esophageal strictures, Barrett's esophagus, and esophageal adenocarcinoma.[3] The range of GERD prevalence estimates were 18.1% to 27.8% in North America and the incidence per 1000 person-years was approximately 5 in the overall UK and US populations.[4] The pathophysiology of GERD is multifactorial, with contributing mechanisms including hiatal anatomic changes (i.e., hiatal hernia), lower esophageal sphincter incompetence, altered frequency of transient lower esophageal sphincter relaxations, esophageal acid exposure, insufficient esophageal motility, delayed gastric emptying, duodeno-gastro-esophageal reflux, and obesity.[5] There is no gold standard for the diagnosis of GERD. The diagnosis may be based on a combination of symptom presentation, endoscopic evaluation of esophageal mucosa, reflux monitoring, and response to therapeutic intervention.[6] The approach to managing GERD is based on symptom presentation, endoscopic findings (e.g., the presence of erosive esophagitis and/or Barrett's esophagus), and physiological abnormalities (e.g., gastroparesis or ineffective motility).

Zollinger-Ellison syndrome (ZES) is characterized by gastric acid hypersecretion from pancreatic or duodenal gastrinomas, which typically leads to GERD,

[1] Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. 2022;117(1):27-56. doi:10.14309/ajg.0000000000001538

[2] https://www.niddk.nih.gov/health-information/digestive-diseases/acid-reflux-ger-gerd-adults/symptoms-causes

[3] Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal Reflux Disease: A Review. JAMA. 2020;324(24):2536-2547. doi:10.1001/jama.2020.21360

[4] El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63(6):871-880. doi:10.1136/gutjnl-2012-304269

[5] Fuchs KH, Lee AM, Breithaupt W, Varga G, Babic B, Horgan S. Pathophysiology of gastroesophageal reflux disease-which factors are important?. Transl Gastroenterol Hepatol. 2021;6:53. Published 2021 Oct 25. doi:10.21037/tgh.2020.02.12

[6] Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. 2022;117(1):27-56. doi:10.14309/ajg.0000000000001538

recurrent peptic ulcers, and chronic diarrhea.[7] 0.5 to 3 out of every 1 million people are diagnosed with ZES each year.[8] The autosomal dominant inherited disease, multiple endocrine neoplasia type 1 (MEN1), is the cause of ZES in 20 to 30% of cases. The pathogenesis of sporadic (i.e., nonherited) gastrinomas in 70 to 80% of patients remains unclear.[9] The diagnosis of ZES is established by documenting gastric acidity and inappropriate hypergastrinemia (i.e., an elevated basal or stimulated gastrin concentration in the presence of an acidic gastric pH≤2).[10]

In the majority of patients, the symptoms and endoscopic signs of GERD resolve with medical treatment, including lifestyle modifications and pharmacologic therapy to reduce or neutralize gastric acid secretion. These medications include proton pump inhibitors (PPIs), histamine H2-receptor antagonists (H2RA), and antacids. PPIs (e.g., lansoprazole, dexlansoprazole, omeprazole, esomeprazole, rabeprazole) are approved for the proposed indications,[11] and are the most commonly prescribed medications for treatment of GERD based on data demonstrating consistently superior heartburn and regurgitation relief, as well as improved healing compared to H2RAs.[12] Surgical or endoscopic treatment is generally recommended for patients who have persistent symptoms or develop complications despite optimal medical therapy.[13]

The management of ZES includes both control of gastric acid hypersecretion and the treatment of the tumor. PPIs are first line treatment for suppressing acid secretion and symptom control. Surgical removal of the primary tumor (and possibly its metastases) with curative intent should be performed. For patients with advanced or metastatic disease, treatment options include systemic medical therapies (e.g., somatostatin analogs, targeted therapies, chemotherapy), peptide-radioreceptor therapy, locoregional therapies (e.g., thermoablation, transarterial chemoembolization, transarterial radioembolization), and surgery.[14]

This application provides for a new dosage form from lyophilized powder (for injection) to a ready-to-use, frozen, premixed solution (injection in sodium chloride injection). Both products are for intravenous administration, but the proposed product does not require reconstitution or additional dilution. The formulations for the proposed product (40 mg/100 mL, 40 mg/50 mL, and 80 mg/100 mL) represent commonly used dilutions of pantoprazole which are similar to the LD following reconstitution and dilution, and provide another option for administering pantoprazole intravenously which may be easier to prepare and administer compared to the LD. Although the proposed product provides the equivalent amount of active ingredient pantoprazole as found in the

[7] Rossi RE, Elvevi A, Citterio D, et al. Gastrinoma and Zollinger Ellison syndrome: A roadmap for the management between new and old therapies. World J Gastroenterol. 2021;27(35):5890-5907. doi:10.3748/wjg.v27.i35.5890
[8] https://www.niddk.nih.gov/health-information/digestive-diseases/zollinger-ellison-syndrome
[9] Metz DC, Cadiot G, Poitras P, Ito T, Jensen RT. Diagnosis of Zollinger-Ellison syndrome in the era of PPIs, faulty gastrin assays, sensitive imaging and limited access to acid secretory testing. Int J Endocr Oncol. 2017;4(4):167-185. doi:10.2217/ije-2017-0018
[10] Metz DC, Cadiot G, Poitras P, Ito T, Jensen RT. Diagnosis of Zollinger-Ellison syndrome in the era of PPIs, faulty gastrin assays, sensitive imaging and limited access to acid secretory testing. Int J Endocr Oncol. 2017;4(4):167-185. doi:10.2217/ije-2017-0018
[11] or indications with similar wording as not all PPIs have the consistently worded indications.
[12] Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. 2022;117(1):27-56. doi:10.14309/ajg.0000000000001538
[13] Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. 2022;117(1):27-56. doi:10.14309/ajg.0000000000001538
[14] Rossi RE, Elvevi A, Citterio D, et al. Gastrinoma and Zollinger Ellison syndrome: A roadmap for the management between new and old therapies. World J Gastroenterol. 2021;27(35):5890-5907. doi:10.3748/wjg.v27.i35.5890

LD following reconstitution and dilution, the proposed product 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.

No bioavailability/bioequivalence (BA/BE), efficacy, or safety studies were conducted by the Applicant for this NDA. The Applicant submitted justification to bridge the proposed drug product to the LD and requested a waiver of in-vivo bioavailability studies. Given the compositional similarity, physicochemical comparability, similarities in the clinical use for administration as an intravenous infusion, and recognizing the linear pharmacokinetics of pantoprazole as demonstrated in the clinical literature and by the Prescribing Information, the Applicant's scientific bridge between the LD and the proposed drug product is established from the biopharmaceutics perspective. The Applicant is relying on the findings of safety and effectiveness of Protonix I.V. and the approved indications.

The benefit-risk assessment of Pantoprazole Sodium in 0.9% Sodium Chloride Injection is unchanged in comparison to the approved LD Protonix I.V. which is currently marketed as safe and effective. There were no new clinical safety issues identified during this review. The labeling is adequate to communicate the known and potential risks of the proposed product, including warnings and precautions unique to the LD as well as PPI class safety concerns, to healthcare providers and patients. The Applicant agreed to a postmarketing requirement (PMR) under the Pediatric Research Equity Act (PREA) to conduct a study to characterize the pharmacokinetics and safety of short-term (at least 4 days) Pantoprazole Sodium in 0.9% Sodium Chloride Injection in pediatric patients aged 1 month to less than 18 years of age requiring treatment for GERD, including patients with a history of erosive esophagitis who require acid suppression therapy and are unable to tolerate oral therapy. A risk evaluation and mitigation strategies (REMS) is not required. Therefore, the labeling, PMR for pediatric patients, and routine pharmacovigilance in the postmarketing setting are adequate to mitigate and monitor known and potential serious safety concerns.

The overall benefit-risk assessment supports approval of Pantoprazole Sodium in 0.9% Sodium Chloride Injection as a new dosage form for short-term treatment (7 to 10 days) of adult patients with GERD associated with a history of EE and for the treatment of pathological hypersecretory conditions including ZE syndrome in adults.

1. Regulatory Background

Pantoprazole is a PPI that suppresses the final step in gastric acid production by covalently binding to the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

A Type B pre-IND meeting, written responses finalized on November 9, 2021, between the Division and the Applicant focused on the proposed biowaiver bridging study strategy, excipient evaluation, and registration stability study design for the product. To support that the "bridge" is scientifically justified, the Division requested that the Applicant provide the following information with justification/supportive data in the NDA submission:

- Qualitative and quantitative composition of the formulations before and after reconstitution/dilution, dosage form, administered volume, labeling, etc., for the proposed drug product and the LD in a side-by-side comparison table.
- Comparative physicochemical data before and after reconstitution/dilution, for at least three production lots of the proposed drug product and three lots of the LD.
- Justification that the use of histidine as a (b) (4) and sodium hydroxide and/or hydrochloric acid as pH adjusters in your proposed product, as opposed to use of only sodium hydroxide in the LD, would not affect product quality and in vivo drug disposition.

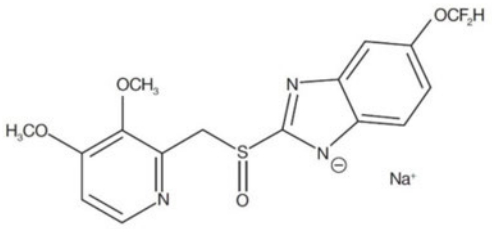
An agreed initial pediatric study plan (iPSP) was reached between the Division and the Applicant on April 27, 2023. Refer to section 9 Pediatrics for further discussion.

2. Product Quality

Drug Substance
The drug substance pantoprazole sodium is a substituted benzimidazole that inhbits the secretion of the gasteric acid. This drug substance was first approved on February 2, 2000 under NDA 020987. Since its initial approval multiple brand name and generic drug products containing this drug substance have been been approved for marketing in the United States.

Pantoprazole sodium is a white to almost white crystalline powder with weak basic and acidic properties. It is freely soluble in water and in ethanol (96 %) and practically insoluble in hexane. Based on X-ray diffraction studies, the pantoprazole sodium drug substance supplied for this application is the Sesquihydrate Form.

Pantoprazole sodium has the chemical name, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole sesquihydrate, the molecular formula, $C_{16}H_{14}F_2N_3NaO_4$. 1.5 H_2O, the molecular weight, 432.39 g/mol, and the chemical structure below:



The drug substance for this application is manufactured in accordance to current Good Manufacturing Practices requirements by (b) (4) It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its proposed retest date of (b) (4) months. The manufacturing information for pantoprazole sodium drug substance supplied for this application is provided in Drug Master File (DMF) (b) (4) This DMF was reviewed and found to be adeqaute to support the approval of this application from the drug substance perspective.

Drug Product

The drug product, Pantoprazole Sodium in 0.9% Sodium Chloride Injection, 40 mg/100 mL, 40 mg/50 mL, and 80 mg/100 mL is a frozen, ready to use, premixed, sterile, iso-osmotice, nonpyrogenic solution supplied in a plastic Galaxy I.V. bag for intravenous administration. Protonix I.V. for Injection which is supplied as lyophilized powder in clear glass vial needing reconstitution and dilution prior to administration is used as the LD for this application. Refer to Table 1 for a comparison of the Applicant's proposed premix product and the LD, Protonix I.V. 40 mg/100 mL.

Table 1: Comparison of the Applicant's Proposed Premix Product and Protonix I.V., 40 mg/100 mL

Attribute	Listed Drug	Applicant's Proposed Premix Product
Product	Protonix IV (vial)	Pantoprazole Sodium in 0.9% Sodium Chloride Injection (bag)
Active Ingredient	Pantoprazole	Same
Total Drug Content[a]	40 mg	Same
Concentration	0.4 mg/mL (upon reconstitution and further dilution)	Same
Dosage Form	Injectable	Same
Route of Administration	Intravenous infusion	Same
Presentation (How Supplied)	Lyophilised powder in a glass vial	Frozen premix solution in a Galaxy container
Reconstitution required	Yes	No

Attribute	Listed Drug	Applicant's Proposed Premix Product
Reconstituted with	10 mL of 0.9% Sodium Chloride	N/A
Dilution required prior to administration	Yes	No
Diluent	Further diluted with: 100 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP	Not applicable as premixed with 0.9% Sodium Chloride
Volume	10 mL upon reconstitution or 100 mL upon reconstitution and further dilution	100 mL
Container Closure System	Single-dose Glass vial	Single-use Galaxy plastic container
Other Inactive Ingredients	Edetate Disodium (1 mg), and Sodium Hydroxide to adjust pH.	Each 100 mL contains: Sodium Chloride (900 mg), Edetate Disodium (1 mg), Histidine (155 mg), (b) (4) and Sodium Hydroxide and/or Hydrochloric Acid to adjust pH
pH (reconstituted solution)	pH range 9.0 to 10.5	N/A
pH of the administered product	Dependent upon which diluent is used for further dilution to 100 mL	9.0 to 10.5
Dosing Regimen and Indication	Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis – 40 mg once daily	Same

[a] 40 mg pantoprazole (equivalent to 45.1 mg of pantoprazole sodium) in the finished product.

Source: Modified from Applicant's Table 6. Comparison of Baxter Proposed Premix and Protonix I.V., 40 mg/100 mL, module 2.3.P Drug Product, pages 10-11/109, submission dated August 17, 2023.

This drug product in addition to pantoprazole sodium as the active ingredient contains the following inactive ingredients: edetate disodium, histidine, hydrochloric acid, sodium chloride, sodium hydroxide, (b) (4). Excipients used in the composition of the drug product are all compendial materials.

The drug product, Pantoprazole Sodium in 0.9% Sodium Chloride Injection, is manufactured in accordance to current Good Manufacturing Practices requirements by Baxter Healthcare Corporation. It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its currently proposed expiration dating period of 12 months.

Pantoprazole sodium is unstable under the thawed conditions and also when it is exposed to light. Therefore, the current storge condition for drug product is store at -20°C (frozen) protected from light for 12 months. The Applicant has provided supporting stability data that show that the thawed drug product is stable for 21 days when stored refrigerated condition of 2°C to 8°C (36°F to 46°F) protected from light. Futhermore, the Applicant has submitted stability data that show the drug product is stable for 48 hours at room temperature 20°C to 25°C (68°F to 77°F).

Biopharmaceutics

Scientific bridge between the proposed product and the LD

The difference in formulation of the proposed product and the LD is the histidine used as a (b) (4) and hydrochloric acid used as a pH adjustor. Histidine is listed on the FDA IID as a component of formulations administered intravenously. It is also routinely delivered intravenously as part of the amino acid component of parenteral nutrition in doses that far exceed the levels found in Pantoprazole Sodium in 0.9% Sodium Chloride Injection. Refer to section 3 Nonclinical Pharmacology/Toxicology for further discussion on histidine. As such, its presence in the formulation will not impact the safety of pantoprazole for the intended indications. Further, differences in the pH adjustor hydrochloric acid (also commonly used in many pharmaceutical products) are not expected to impact the in vivo performance of pantoprazole.

In summary, given the compositional similarity, physicochemical comparability, similarities in the clinical use for administration as an intravenous infusion, and recognizing the linear pharmacokinetics of pantoprazole described in the Prescribing Information of the LD[15], the Applicant's scientific bridge between the LD and the proposed drug product is established from the biopharmaceutics perspective.

The Office Pharmaceutical Quality (OPQ) recommendation:

- The Applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, pantoprazole sodium, and drug product, Pantoprazole Sodium in 0.9% Sodium Chloride Injection, 40 mg/100 mL, 40 mg/50 mL, and 80 mg/100mL.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application. No facility inspections were conducted. The facilities were approved based on previous history.
- The CMC revisions on labels/labeling have been communicated to the Applicant and the recommended CMC revisions have been accepted by the Applicant.
- The Applicant's request for categorical exclusion from preparation of environmental assessment has been found adequate and is granted.

Therefore, from the OPQ perspective this application is recommended for approval with an expiration dating period of 12 months.

[15] https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020988s069lbl.pdf

Refer to the integrated review by Hamid Shafiei, PhD, dated January 30, 2024, for further discussion.

3. Nonclinical Pharmacology/Toxicology

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 I.V., the LD.

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 I.V. 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.

Histidine

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 Table 2.

Table 2: 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 (MDE IID) 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.

Source: Applicant's submission, 3.2.P.1 Description and Composition of the Drug Product, page 4/6.

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 in 0.9% Sodium Chloride Injection as shown in Table 3.

Table 3: Maximum Daily Intake (MDI) of Histidine from Pantoprazole Sodium in 0.9% Sodium Chloride Injection Compared to FDA 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. 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] 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.

Source: Applicant's submission, 3.2.P.1 Description and Composition of the Drug Product, page 5/6.

Sodium Hydroxide and/or Hydrochloric Acid

The inactive ingredients of sodium hydroxide and/or hydrochloric acid may be used to adjust pH in the proposed product. The thawed solution of Pantoprazole Sodium in 0.9% Sodium Chloride injection is in the pH range 9.0 to 10.5. The LD contains the inactive ingredient of sodium hydroxide to adjust pH and the reconstituted solution is in the same pH range 9.0 to 10.5. The LD can be administered as a reconstituted solution without further dilution or a further diluted product in which the pH will be dependent upon which diluent is used for further dilution to 100 mL (5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection). The justification for the use of sodium hydroxide and/or hydrochloric acid as pH adjusters in the proposed product, as opposed to use of only sodium hydroxide in the LD, is that hydrochloric acid is commonly used in many pharmaceutical products for this purpose and is not expected to impact the in vivo performance of pantoprazole.

Impurities

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.

Refer to the pharmacology/toxicology review by Achinto Saha, Ph.D. in DARRTS for additional discussion.

4. Clinical Pharmacology

No clinical pharmacology studies were conducted by the Applicant or submitted for review.

5. Clinical Microbiology

Not applicable

6. Clinical/Statistical-Efficacy

No efficacy studies were conducted by the Applicant to support the efficacy of the proposed product.
The proposed product is relying upon the Agency's findings of efficacy and safety of Protonix I.V.

7. Safety

No safety studies were conducted by the Applicant to support the safety of the proposed product. The proposed product is relying upon the Agency's findings of safety and efficacy of Protonix I.V.

To support the NDA, the Sponsor conducted a literature search in Embase (1996 to 2023 March 03) and MEDLINE (1996 to February Week 4 2023). Data available in published literature support the safety of pantoprazole and pantoprazole sodium for the proposed indications. There were no new clinical safety issues identified during the review of the submitted literature and no other safety information was identified by the review team.

Submission Specific Safety Concerns

Histidine

The level of histidine in the proposed product exceeds the level listed in the FDA IID for the intravenous route of administration based on the MDI. However, the safety of the level of histidine in the proposed product is justified by the presence of histidine in other FDA approved drug products at levels up to 18-fold higher than the level in Pantoprazole Sodium in 0.9% Sodium Chloride Injection.

Although the proposed product is not approved for pediatric use, the amount of histidine in the proposed product appears to be safe for pediatric patients in future studies or off-label use. There are amino acid solutions approved for use in pediatric patients containing histidine (e.g., Prosol [amino acids] injection [16] and Travasol [amino acids injection][17]). Prosol contains the essential amino acid histidine at a concentration of 1.18 g/100 mL. The recommended daily dose of Prosol for parenteral nutrition in preterm and term infants less than 1 month of age is 15 to 20 mL/kg/day. An average neonate of 3.5 kg would therefore receive 52.5 to 70 mL/day or 619.5 to 826 mg of histidine. The MDI of histidine in Pantoprazole Sodium in 0.9% Sodium Chloride Injection, based on a maximum daily dose of pantoprazole of 80 mg intravenously every 8 hours for adults with pathological hypersecretion conditions including Zollinger-Ellison Syndrome, is 465 mg of histidine, which is a lower MDI of histidine that a neonate would receive from administration of Prosol. The recommended daily dosage of Prosol for parenteral nutrition in stable and critically ill adults results in much higher doses of histidine, with a MDI of 8260 mg of histidine, based on a maximum dose of Prosol of 10 mL/kg/day in a 70 kg critically ill adult. Therefore, the amount of histidine in the proposed product is expected to be safe for pediatric patients in future studies, given the higher amount of histidine in parenteral nutrition products approved for use in pediatric patients.

A literature review did not reveal any information that the proposed amount of histidine (155 mg) would be concerning for pediatric or adult patients, or affect product quality and in vivo drug disposition. At high intakes of histidine (>24 g/d), studies report adverse effects of histidine such as decreased serum zinc and cognitive impairment. There is limited research on the effects of histidine intake at doses between 4.5 and 24 g/d, and thus, a tolerable upper level has not been established. At low doses (e.g., ≤4.5 g/d), histidine supplementation appears to be well tolerated among healthy and clinical populations.[18]

The CMC and nonclinical reviews did not identify safety concerns for the amount of histidine in the proposed product.

Refer to section 3 Nonclinical Pharmacology/Toxicology for additional discussion.

Edetate disodium

Pantoprazole Sodium in 0.9% Sodium Chloride Injection contains edetate disodium (the salt form of EDTA), a chelator of metal ions including zinc. The amount of EDTA in the proposed product is the same as Protonix I.V., the LD, as shown in Table 4.

[16] Prosol: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020849s025lbl.pdf
[17] Travasol: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/018931s055lbl.pdf
[18] Thalacker-Mercer AE, Gheller ME. Benefits and Adverse Effects of Histidine Supplementation. J Nutr. 2020;150(Suppl 1):2588S-2592S. doi:10.1093/jn/nxaa229

Table 4: Comparison of Edetate Disodium in the LD and Proposed Product

	Listed drug: Protonix I.V., NDA 020988	**Proposed product: Pantoprazole Sodium in 0.9% Sodium Chloride Injection**
Concentration	0.4 mg/mL and 0.8 mg/mL (upon reconstitution and further dilution)	Same (No reconstitution and dilution required)
Inactive Ingredient	For 40 mg per vial: Edetate disodium (1 mg)	For 0.4 mg/mL: Each 100 mL contains edetate disodium (1 mg)
	For 80 mg per 2 vials: Edetate disodium (2 mg)	For 0.8 mg/mL: Each 100 mL contains edetate disodium (2 mg)

Source: Modified from the Applicant's submission, 2.5 Clinical Overview, Table 1. Comparison of the Proposed Baxter Product and Protonix I.V., pages 6-7/40.

The maximum daily intake[19] (6 mg) of EDTA in the proposed product is less than the maximum daily exposure based on IID levels for the intravenous route of administration[20] (19 mg), as shown in Table 1. Although the proposed product is not approved for pediatric use, the amount of EDTA in the proposed product appears to be safe for pediatric patients in future studies or off-label use. The relative amount of EDTA in the proposed product is comparable to or less than the dose of EDTA delivered from other approved I.V. products for pediatric use as noted in Table 5.

Table 5: IV Drug Products Containing EDTA Approved for Pediatric Use

Drug product	**Content**	**Maximum daily dose of DP in pediatric patients**	**Daily exposure to EDTA[1]**
Nexium	1.5 mg EDTA for each 20 mg esomeprazole	20 mg > 55 kg 10 mg < 55 kg 0.5 mg/kg < 1 month	Up to 1.5 mg
Zosyn	0.5 mg EDTA for each 2g of piperacilin	100 mg/kg, every 8h 1800-9000 mg/day	0.45-2.25 mg/day
Diprivan	5 mg EDTA per 100 mL propofol	2.5-3.5 mg/kg 21-105 mg/day	1-5 mg/day
Amphotec	5.64 mg/50 mg vial 11.28 mg/100 mg vial	Administered in children from 3 to 16 years old; 3-4 mg/kg once a day, similar with adult dose	4.5-23.4 mg/day
Cleocin phosphate	0.5 mg for each 150 mg clindamycin	Indicated in children from birth to 16 years old First dose: 5-7 mg/kg IV in 1 hour, then 15-20 mg/kg/day in 3 to 4 equal doses – less than 1 month, or 20-40 mg/kg/day in 3 or 4 equal doses – 1 month to 16 years	Up to 8.1 mg/day
Dexamethasone sodium phosphate	0.11 mg EDTA for 4.4 mg dexamethasone	3 mg/kg/day as cont IV infusion, after an initial IV inj of 20 mg	Up to 4.4 mg/day

[19] 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.
[20] http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

Drug product	Content	Maximum daily dose of DP in pediatric patients	Daily exposure to EDTA[1]
Depacon	0.4 mg EDTA for each 100 mg valproic acid	60 mg/kg/day 1800 mg/day	Up to 7.2 mg
Aloxi	2.5 mg EDTA for 0.25 mg palonosetron	Indicated in children from 1 month to less than 17 years 20 µg/kg (max 1.5 mg)	15 mg

[1] The weight is calculated according to the WHO standards, as follows: 6 kg bodyweight for a 6 month patient, 10 kg for a 3 year old, 30 kg for a 12 year old, 52 kg for a 16 year old.

Source: Modified from NDA 210064 Fosaprepitant for Injection, clinical review by Sandhya Apparaju, Ph.D., dated 09/08/2017, Table 5 IV Drug Products Containing EDTA Approved for Pediatric Use, page 36/53.

Infusion rates

The infusion rates were compared between the LD and Pantoprazole Sodium in 0.9% Sodium Chloride Injection to ensure similar systemic exposure.

The LD (Protonix I.V.) is supplied as 40 mg powder in a single-dose vial for reconstitution.

- GERD Associated with EE: 40 mg once daily IV
  Once reconstituted and further diluted, the final concentration is 0.4 mg/mL administered IV over 15 minutes at a rate of approximately 7 mL/min.
    - Infusion rate - 2.8 mg/min
- Pathological Hypersecretion Conditions, Including ZE Syndrome: 80 mg every 12 hours IV
  15-minute infusion: Once reconstituted and further diluted, the final concentration is 0.8 mg/mL administered IV at a rate of approximately 7 mL/min.
    - Infusion rate - 5.6 mg/min
- 2-minute infusion: Once reconstituted, without further dilution, the final concentration is 4 mg/mL administered the total volume from both vials (20 mL) over at least 2 minutes, rate of 10 mL/min.
    - Infusion rate – 40 mg/min

Pantoprazole Sodium in 0.9% Sodium Chloride Injection

- 40 mg/100 mL (0.4 mg/mL)
- 40 mg/50 mL (0.8 mg/mL)
- 80 mg/100 mL (0.8 mg/mL)

These pre-mixed formulations represent commonly used dilutions of pantoprazole which are similar to the LD following reconstitution and dilution.

- Both indications, 15-minute infusion
  The final concentration is 0.4 mg/mL or 0.8 mg/mL administered IV at a rate of 6.7 mL/min (100 mL volume) or 3.3 mL/min (50 mL volume).
    - Infusion rates – 2.7 mg/min (40 mg/100 mL, 40 mg/50 mL), 5.4 mg/min (80 mg/100 mL)

Therefore, the infusion rates of Pantoprazole Sodium in 0.9% Sodium Chloride Injection are within the range of the LD (2.8 to 40 mg/min) and no pharmacokinetic differences from the LD are expected.

Pregnancy and Lactation Labeling Rule

The Applicant conducted a literature search to identify any new information related to pantoprazole use during pregnancy and lactation, and any effects of pantoprazole on male and female fertility up to April 2023. As per the Applicant, "no publications were identified which would result in the need to update the prescribing information for pregnancy and lactation in the drug relied upon, Protonix I.V.." The Applicant's draft prescribing information (PI) for Pantoprazole Sodium in Sodium Chloride Injection is consistent with Protonix I.V..

Protonix I.V. was converted to the Pregnancy and Lactation Labeling Rule (PLLR) format with NDA 022020/S-017 approved on April 25, 2019. A Division of Pediatric and Maternal Health (DPMH) reviewer at that time reviewed the available relevant data on pantoprazole from published literature. The findings were incorporated into the approved Protonix I.V. labeling. For the current application for Pantoprazole Sodium in Sodium Chloride Injection, DPMH performed an updated search of the published literature from April 2019 to the present and did not identify any new safety information. Available data from published observational studies did not demonstrate an association of major birth defects, miscarriage, or other adverse maternal or fetal outcomes with pantoprazole. Limited data from a single case reports the presence of pantoprazole in human breast milk. DPMH provided minor labeling recommendations to reflect current PLLR labeling practices on December 12, 2023; however, the draft PI remains mostly consistent with Protonix I.V. labeling.

8. Advisory Committee Meeting

This application for Pantoprazole Sodium in 0.9% Sodium Chloride Injection was not referred to an FDA advisory committee because this drug is not the first in its class.

9. Pediatrics

An agreed initial pediatric study plan (iPSP) was reached between the Division and the Applicant on April 27, 2023. For GERD with history of EE, the Applicant requested a partial waiver for pediatric patients birth to less than 1 month of age due to necessary studies being impossible or highly impracticable. The Applicant requested a deferral for patients 1 month to less than 18 years of age to evaluate the PK and safety of short-term (at least 4 days) I.V. pantoprazole in pediatric patients with GERD, including patients with a history of EE. This deferral is due to (1) the proposed drug product will be ready for submission for use in adults before pediatric studies are complete as the adult program plans to rely upon the LD Protonix I.V., and additional clinical studies in adults are not planned, and (2) (b) (4)

(b) (4)

(b) (4)

For pathological hypersecretion conditions including ZE Syndrome, the Applicant requested a full waiver for pediatric patients birth to less than 18 years of age due to the rare incidence of pathological hypersecretion conditions including ZE Syndrome in children, resulting in necessary studies being impossible or highly impracticable.

The pediatric review committee (PeRC) discussed the Applicant's requests on January 9, 2024 and agreed to grant full waiver for ZE and partial waiver for GERD for pediatric patients birth to less than 1 month of age. The PeRC agreed to the proposed PREA PMR to study GERD in pediatrics 1 month to less than 18 years of age. Refer to the PeRC meeting minutes, dated January 31, 2024, in DARRTS.

PREA PMR 4578-1

Conduct a study to characterize the pharmacokinetics and safety of short-term (at least 4 days) Pantoprazole Sodium in 0.9% Sodium Chloride Injection in pediatric patients aged 1 month to less than 18 years of age requiring treatment for gastroesophageal reflux disease, including patients with a history of erosive esophagitis who require acid suppression therapy and are unable to tolerate oral therapy.

Draft Protocol Submission:	06/2028
Final Protocol Submission:	12/2028
Study/Trial Completion:	12/2033
Final Report Submission:	06/2034

Additional bridging information may be requested depending on the pediatric data available to the Applicant at the time of protocol submission.

10. Other Relevant Regulatory Issues

The 505(b)(2) committee has cleared this application for approval under the regulations.

Financial certification and disclosure are not applicable for this 505(b)(2) NDA application.

There are no patents remaining for the LD.

11. Labeling

Prescribing Information

Prescribing information for this proposed product is based on LD labeling. Product specific information is included in the CMC section and the LD trade name was replaced with the established name of the proposed drug product. See Table 6 for a summary.

Table 6: Summary of Prescribing Information

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to the Applicant's Proposed Draft PI
INDICATIONS AND USAGE	Per the product naming convention recommended by OPQ, when referring to the Applicant's product, use title case (i.e., Pantoprazole Sodium in 0.9% Sodium Chloride Injection) throughout the PI.
DOSAGE AND ADMINISTRATION	This section was updated to reflect use of the Applicant's ready to use product that is manufactured in volumes reflective of those appropriate for administration via a 15 minute infusion.
DOSAGE FORMS AND STRENGTHS	Deleted (b) (4) (b) (4) (b) (4), as only limited packaging information is needed in this section. Deleted the (b) (4) (b) (4) which are only needed in Section 11. Added a description of identifying characteristics of the dosage form "Thawed solutions are clear and range from colorless to yellow over time."
WARNINGS AND PRECAUTIONS	This section includes PPI class Warnings and Precautions as well as those unique to Protonix (and not PPIs in general), which include injection site reactions, potential for exacerbation of zinc deficiency, and hepatic effects. Section 5.2 Injection Site Reactions was updated to state that "Thrombophlebitis was reported in association with the administration of another intravenous pantoprazole sodium product." Section 5.3 Potential for Exacerbation of Zinc Deficiency was retained as the amount of EDTA in the proposed product is the same as Protonix I.V. Section 5.9 Hepatic Effects was updated to state that "Mild, transient transaminase elevations have been observed in clinical studies with another intravenous pantoprazole sodium product."
ADVERSE REACTIONS	Because the studies described in this section were conducted with the LD and not the Applicant's proposed product, the following statement has been added to describe the data. "The safety of Pantoprazole Sodium in 0.9% Sodium Chloride Injection has been established from adequate and well controlled studies of another intravenous pantoprazole sodium product *[see Clinical Studies (14)]*. Below is a display of the adverse reactions of pantoprazole sodium in these adequate and well controlled studies."
USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	In section 8.2 Lactation, the first sentence was revised to include specific information from the literature, stating "The limited data from a single case reports the presence of pantoprazole in human breast milk." Removed the Animal Toxicity Data subsection from (b) (4) (b) (4) as that is not the appropriate place for this information. The pre- and post-natal development toxicity study in rats is already discussed in Section 8.1 under Animal Data.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to the Applicant's Proposed Draft PI
	(b) (4) (b) (4) In section 8.5 Geriatric Use the following statement was added (based on a similar statement in section 12.3 Clinical Pharmacology). "No clinically meaningful differences in the pharmacokinetics of pantoprazole were observed in geriatric subjects compared to younger adult subjects *[see Clinical Pharmacology (12.3)]*."
CLINICAL PHARMACOLOGY	In section 12.5 Pharmacogenomics, removed (b) (4) (b) (4) (b) (4) "Following oral administration patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers."
CLINICAL STUDIES	Because the studies described in section 14 were conducted with the LD and not the Applicant's proposed product, the following statement has been added to describe the data. "The safety and efficacy of Pantoprazole Sodium in 0.9% Sodium Chloride Injection have been established based on adequate and well-controlled adult studies of another intravenous pantoprazole sodium product in GERD associated with a history of EE and pathological hypersecretory conditions, including Zollinger-Ellison syndrome. Below is a display of the results of these adequate and well-controlled studies of pantoprazole sodium in these conditions."
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Revised Table 6. Supply Information for Pantoprazole Sodium in 0.9% Sodium Chloride Injection to include the the strength based on active moiety (pantoprazole). The codes are not needed and have been removed from the table.\ Added "Thawed solutions are clear and range from colorless to yellow over time" to provide a visual description of the product.

Source: Reviewer's table
[1] Some sections may not be included because those sections may not have major issues (or changes).
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): PI, Prescribing Information

The Applicant accepted the labeling changes detailed above, with the exception of the review team's recommendation to remove the brand name of the container because flexible containers are made by multiple manufacturers and there is nothing unique about the Galaxy brand. The review team agreed to permit the Applicant to use the Galaxy brand as there are other approved products using this brand name.

There are no patient labeling documents associated with this product.

12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

REMS are not required.

- Postmarketing Requirements and Commitments

The Applicant agreed to conduct the PREA PMR 4578-1 with the timelines listed below.

PREA PMR 4578-1

Conduct a study to characterize the pharmacokinetics and safety of short-term (at least 4 days) Pantoprazole Sodium in 0.9% Sodium Chloride Injection in pediatric patients aged 1 month to less than 18 years of age requiring treatment for gastroesophageal reflux disease, including patients with a history of erosive esophagitis who require acid suppression therapy and are unable to tolerate oral therapy.

Draft Protocol Submission:	06/2028
Final Protocol Submission:	12/2028
Study/Trial Completion:	12/2033
Final Report Submission:	06/2034

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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02/13/2024 02:43:08 PM

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