Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	20988
Priority or standard	Standard
Submit date(s)	10/31/2023
Received date(s)	10/31/2023
PDUFA goal date	8/31/2024
Division/office	Division of Gastroenterology (DG)
Review completion date	8/12/2024
Established/proper name	Pantoprazole sodium
(Proposed) proprietary name	Protonix® I.V. (pantoprazole sodium) for injection, for Intravenous Use
Pharmacologic class	Proton Pump Inhibitor
Other product name(s)	Not Applicable
Applicant	Wyeth Pharmaceuticals LLC
Dosage form(s)/formulation(s)	Injection, powder, (b) (4) for solution
Applicant-proposed dosing regimen	(b) (4) to less than 1 year of age: 0.8 mg/kg with maximum dose of 10 mg QD 1 year to 17 years: • Body weight 15 kg or less: 10 mg QD • Body weight greater than 15 kg to 40 kg or less: 20 mg QD • Body weight greater than 40 kg: 40 mg QD
Applicant-proposed indication(s)/ population(s)	Short-term (up to 7 days) treatment of pediatric patients aged (b) (4) and older with gastroesophageal reflux disease and a history of erosive esophagitis
SNOMED CT code for proposed indication disease term(s)[1]	235595009
Regulatory action	Approval
Approved dosage	3 months to less than 1 year of age • Less than 12.5 kg: 0.8 mg/kg once daily • 12.5 kg and above: 10 mg once daily 1 year to 17 years of age • Up to 15 kg: 10 mg once daily • Greater than 15 kg up to 40 kg: 20 mg once daily • Greater than 40 kg: 40 mg once daily
Approved indication(s)/ population(s) (if applicable)	For the treatment of gastroesophageal reflux disease and a history of erosive esophagitis for up to 7 days in pediatric patients 3 months and older
SNOMED CT code for approved indication disease term(s)[1]	235595009

[1] For internal tracking purposes only.
Abbreviation(s): PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AE	adverse event
AUC	area under the concentration-time curve
AWC	adequate and well-controlled
BW	body weight
CL	clearance
CM	Clinical Modification
C_{max}	maximum plasma concentration
CFR	Code of Federal Regulation
DEPI	Division of Epidemiology
DR	delayed-release
DRESS	drug reaction with eosinophilia and systemic symptoms
EE	erosive esophagitis
EHR	electronic health records
FDA	Food and Drug Administration
GERD	gastroesophageal reflux disease
ICD	International Classification of Diseases
IR	incidence rate
IV	intravenous
NDA	new drug application
NDC	National Drug Codes
NOAEL	no observed adverse effect level
PD	pharmacodynamic
PI	prescribing information
PK	pharmacokinetic
PMR	postmarketing requirement
PND	postnatal day
PopPK	population pharmacokinetics
PPI	proton pump inhibitor
PREA	Pediatric Research Equity Act
QD	once daily
SAE	serious adverse event
SEE	substantial evidence of effectiveness
SJS	Stevens-Johnson syndrome
SOI	safety outcomes of interest
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
URI	upper respiratory tract infection
y/o	year(s) old

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

On October 31, 2023, Wyeth ("the Applicant") submitted a supplemental new drug application (NDA 20988/S-070), seeking the approval of Protonix IV (pantoprazole sodium) for injection for the short-term intravenous (IV) treatment (up to 7 days) of gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis (EE) in pediatric patients (b) (4) and older. The submission included findings from Study B1791089, an open-label, pharmacokinetic (PK) and safety study of IV pantoprazole in pediatric subjects 1 to 16 years of age. Additionally, the Applicant included a population pharmacokinetics (PopPK) model to support the exposure comparison between pediatric subjects 1 month to 16 years of age and adults, legacy Wyeth pediatric studies (IV and oral)[1] that were previously reviewed under NDA 22020 (S-001/S-002; Sequence #020) for oral pantoprazole, published literature, and post-marketing safety database findings to support the pediatric indication. Results from Study B1791096, a retrospective cohort study using electronic health records (EHR) to assess the safety of pantoprazole IV in pediatric patients 1 month to <1 year, and 1 to <2 years of age were also included with this submission. This supplemental NDA was reviewed by a multidisciplinary review team and all disciplines have recommended approval. The signatory authority for this application concurs with those recommendations.

The use of Protonix IV for up to 7 days in pediatric patients 3 months of age and older relies on extrapolation of efficacy[2] data from adequate and well-controlled clinical trials that supported approval of IV and oral pantoprazole in adults and oral pantoprazole in pediatric subjects[3] with EE associated with GERD, together with additional PK and safety data of IV pantoprazole in pediatric subjects at least 1 year of age and oral pantoprazole in pediatric subjects at least 1

[1] Study Wyeth 3001B3-333-WW (PK, PD, and safety study of oral pantoprazole in infants 1 to 11 months of age with presumed GERD); Study 3001B3-329-WW (efficacy and safety study of oral pantoprazole in infants 1 to 11 months of age with symptomatic nonerosive GERD); Study 3001K1-117-US (PK, PD and safety study of IV pantoprazole in pediatric subjects 1 to <2 years who were candidates for acid suppression therapy); Study 3001K1-110-US (PK, PD, and safety of IV pantoprazole in pediatric subjects 2 to 16 years who were candidates for acid suppression therapy); Study 3001B3-328-NA (efficacy and safety study or oral pantoprazole in pediatric subjects 1 to 5 years with symptomatic GERD and EE); Study 3001A1-322-US (efficacy and safety study of oral pantoprazole in pediatric subjects 5 to 11 years with symptomatic GERD and EE).

[2] See the draft guidance for industry *E11A Pediatric Extrapolation* (April 2022) (https://www.fda.gov/media/161190/download). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] The safety and effectiveness of Protonix for short-term treatment (up to eight weeks) of EE associated with GERD have been established in pediatric patients 1 year through 16 years of age. For patients less than 5 years of age, there is no appropriate dosage strength in an age-appropriate formulation available. Therefore, Protonix is indicated for the short-term treatment of EE associated with GERD for patients 5 years and older. See approved product labeling: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020987s060,022020s023lbl.pdf

month of age. Study B1791089 demonstrated similar exposure between pediatric subjects 1 year and older following the proposed dosing regimen and adults following the approved dosing regimen. Additionally, a comparable PK/pharmacodynamic (PD) relationship (median gastric pH and %Time pH >4) in infants <1 year of age receiving oral pantoprazole to adults receiving IV/oral pantoprazole provided support for approval in this age group; however, for infants 1 to <3 months of age, the PK of IV pantoprazole could not be reliably predicted in pediatric patients <3 months of age, and therefore, extrapolating efficacy of pantoprazole to infants <3 months of age was not supported. In general, the disease pathogenesis and response to treatment with PPIs are sufficiently similar between adult and pediatric populations with EE. Additionally, pantoprazole is a proton pump inhibitor, a drug class with multiple approved products for which data are available from both adult and pediatric trials that provide for a well understood mechanism of action for treating acid-mediated diseases including GERD with EE and symptomatic non-erosive GERD, and a well characterized safety profile. Therefore, there is a substantial level of confidence in the available evidence to support relying on extrapolation of efficacy to expand the indication for IV pantoprazole to include treatment of GERD with a history of EE for up to 7 days in pediatric patients 3 months and older. The evidence from adult and pediatric studies, through extrapolation, provides for substantial evidence of effectiveness (SEE) for up to 7 days of treatment with IV pantoprazole in pediatric patients who are 3 months of age and older with GERD associated with a history of EE.

Safety following single and multiple (4 to 7 days) of IV pantoprazole was evaluated in Study B1791089 in hospitalized pediatric subjects 1 to 16 years of age who were candidates for acid suppression therapy and was supported by findings from legacy trials in pediatric subjects following oral and IV routes of administration. The dosing regimens evaluated in Study B1791089 were either similar to or higher than the proposed dosing regimens. Therefore, the studied dosing regimens in pediatric subjects 1 year and older across the three body weight cohorts provided adequate exposure coverage to support the safety evaluation for the proposed dosing regimens. Of note, infants (<1 year of age) were not enrolled in Study B1791089. Safety in infants was supported by data from a legacy trial of oral pantoprazole in infants <1 year of age with symptomatic nonerosive GERD (not a labeled indication in this age group[4]), comparable safety of pantoprazole in pediatric subjects 1 to <2 years of age following oral and IV administration despite differences in C_{max} (observed in the legacy studies), and safety data leveraged from adults and older pediatric cohorts[2] to infants <1 year of age, in particular to support the predicted higher C_{max} values in infants <1 year of age. Additionally, adequate safety margins for the predicted PK of IV pantoprazole in infants <1 year of age have been demonstrated in the juvenile animal studies. Although only one subject with EE was enrolled in the pediatric PK study and none in the legacy trial in infants, EE is a subtype of GERD, and the severity of the disease and presence of erosions are not expected to significantly affect the safety of this product and the known safety profile of the drug class overall. No evidence of differential safety in pediatric subjects was noted within subgroups of patients with GERD with or without EE in legacy studies of oral pantoprazole. An observational study, B1791096, provided additional support for the safety of IV pantoprazole in infants and subjects 1 to <2 years of age. Safety of pantoprazole is well established in adults following oral and IV routes of

[4] While oral Protonix, along with other drugs in the proton pump inhibitor class, did not demonstrate efficacy in infants <1 year of age with symptomatic nonerosive GERD, data from a completed clinical trial of oral pantoprazole in this population did not raise any unique safety concerns in this age group.

administration and in pediatric patients following an oral route. Safety of Protonix IV in pediatric patients is supported for the proposed duration of use for up to 7 days.

The review team thus recommends the approval of Protonix IV for the treatment of GERD and a history of EE for up to 7 days in pediatric patients 3 months and older. The recommended dosing regimen by age and body weight strata is shown below in Table 2. All doses are intended for administration as IV infusions over 15 minutes, once daily for a duration of up to 7 days.

Table 2. Recommended Pediatric Dosage Regimen for GERD and a History of EE

Age	Body Weight	Dosage Regimen (up to 7 Days)
3 months to less than 1 year of age	Less than 12.5 kg	0.8 mg/kg once daily
	12.5 kg and above	10 mg once daily
1 year to 17 years of age	Up to 15 kg	10 mg once daily
	Greater than 15 kg up to 40 kg	20 mg once daily
	Greater than 40 kg	40 mg once daily

Source: Reviewer generated adapted from the recommendations in the prescribing information
Abbreviation(s): EE, erosive esophagitis; GERD, gastroesophageal reflux disease

The approval of this supplemental application for Protonix IV fulfills the previously deferred Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) 255-6 and 145-1. Additionally, a partial waiver requested by the Applicant will be granted for studies in neonates (<1 month of age) as studies are impracticable in this subgroup. See Section 8.3.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with evidence that supported SEE from a prior approval.[5]

Protonix IV is approved in adults for a short-term treatment (7 to 10 days) of GERD associated with a history of EE. Protonix is also approved for oral use for the short-term *(up to 8 weeks)* treatment of EE associated with GERD and for the maintenance of healing of EE in adults. It is also approved for the short-term *(up to 8 weeks)* treatment of EE associated with GERD in children 5 years and older. The data from pediatric clinical trials supported use of oral Protonix in pediatric patients down to 1 year of age; however, due to the absence of a commercial dosage form in younger patients, the product was labeled for pediatric patients 5 years and older.

SEE for Protonix IV for the treatment of GERD and a history of EE for up to 7 days in pediatric patients 3 months and older was established with evidence from adequate well controlled trials of IV and oral pantoprazole in adults and oral pantoprazole in pediatric patients with EE associated with GERD, together with additional PK data of IV pantoprazole in pediatric patients 1 year of age and older and supplemented by data from clinical trials of oral pantoprazole in pediatric patients 1 month to <1 year of age.

[5] SEE was established by available evidence that supported prior approvals of Protonix for IV and oral use in adult and pediatric patients.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 3. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• GERD is a condition where the reflux of gastric contents into the esophagus results in symptoms and/or complications. GERD can present as symptomatic nonerosive GERD (NERD) or EE. • Common symptoms of GERD include heartburn and regurgitation. GERD has varying symptoms in infants and younger children, such as feeding difficulties, regurgitation, vomiting and poor weight gain. EE, a complication of GERD, becomes more common with age. A retrospective cross-sectional study of pediatric patients undergoing upper endoscopy reported EE in 5.5% of infants, and the prevalence progressively increased to 19.6% of children by 17 years.[6] • Complications of GERD, if inadequately treated, can include esophagitis, esophageal strictures, Barrett's esophagus, and esophageal adenocarcinoma.	• GERD can have a signfiicant impact on the overall well being, nutrition, and growth of pediatric patients. EE is a complication of GERD. The goals of treating EE in pediatric patients include healing of erosions, reducing symptoms, and maintaining healing of erosions and mitigating the potential for complications of acid-mediated damage to the esophagus in the long-term.

[6] M Gilger, H El-Serag, B Gold, C Dietrich, V Tsou, A McDuffie, and M Shub, 2008, Prevalence of Endoscopic Findings of Erosive Esophagitis in Children: A Population-Based Study, J Pediatr Gastroenterol Nutr, 47(2):141-146.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Management of GERD is based upon symptoms and endoscopic findings and include dietery changes, lifestyle modifications, and use of antacids and pharmacologic therapy to reduce gastric acid secretion. • Available treatment options to relieve symptoms and promote healing of esophagitis include H2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs). • PPIs approved for oral use in pediatric patients include omeprazole, esomeprazole, lansoprazole, dexlansoprazole, and pantoprazole and differ in the indication(s) and age range(s) for which they are approved. • Currently only Nexium IV is approved for intravenous use in pediatric patients and is the only PPI product approved for use in infants (1-11 months of age).	• PPIs remain the mainstay in the treatment of GERD and EE in pediatric patients. There remains a need for age-appropriate formulations of PPIs, including IV formulations for the management of GERD and EE in pediatric patients, including infants who are unable to use oral treatments.
Benefit	• Efficacy of Protonix IV relied on extrapolation of efficacy data from adequate and well-controlled clinical trials of pantoprazole (IV and oral) in adults and oral pantoprazole in pediatric patients 1 year of age and older[3], with additional PK data of IV pantoprazole in pediatric patients 1 year of age and older, and oral pantoprazole in pediatric patients 3 months of age and older. Study B1791089 demonstrated similar exposure between pediatric subjects 1 year and older following the proposed dosing regimen and adults following the approved dosing regimen. Additionally, a comparable PK/pharmacodynamic relationship (median gastric pH and %Time pH >4) in infants <1 year of age receiving oral pantoprazole to adults receiving IV/oral pantoprazole provided support for approval in this age group; however, the PK of pantoprazole IV could not be reliably predicted in pediatric patients <3 months of age.	• Overall the disease pathogenesis and response to treatment with PPIs are sufficiently similar between adult and pediatric populations with EE. The efficacy of PPIs, including pantoprazole, has been well established for the treatment of GERD with a history of EE in adult and peditric patients for over two decades. There is a substantial level of confidence in the available evidence to support relying on extrapolation of efficacy from clinical trials that supported approval of pantoprazole (IV and oral) in adults and oral pantoprazole in pediatric patients. • Study B1791089 demonstrated similar exposure between pediatric subjects 1 year and older and adults. For infants 1 to <3 months of age, the PK of pantoprazole IV could not be reliably predicted in pediatric patients <3 months of age, and therefore, extrapolating efficacy of pantoprazole to infants <3 months of age was not supported. Thus, the approval of Protonix IV will be limited to pediatric patients 3 months and older.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• Study B1791089 assessed the safety of Protonix IV (once daily for 4 to 7 days) in pediatric subjects 1 to 16 years of age. The dosing regimens evaluated in Study B1791089 were either similar to or higher than the proposed dosing regimens. Therefore, the studied dosing regimens in pediatric subjects 1 year and older across the three body weight cohorts provided adequate exposure coverage to support the safety evaluation for the proposed dosing regimens. The safety of IV pantoprazole was generally consistent with that in adults. Legacy studies of IV pantoprazole, as well as oral pantoprazole in pediatric patients including infants <1 year of age, supported by PK exposure comparisons, provided additional support for safety. An observational study, B1791096, provided additional safety information for IV pantoprazole in infants <1 year of age and patients 1 to <2 years of age. The safety of PPIs, including pantoprazole, for the treatment of GERD and a history of EE has been well understood for over two decades. Furthermore, the safety profile for a duration of use over 7 days is expected to be similar to what is generally known for pantoprazole.	• The safety of of Protonix IV for up to 7 days of use is adequately supported in pediatric patients including infants at least 3 months of age. • The labeling will include a statement to discontinue IV treatment as soon as the patient is able to tolerate oral treatment. • The label will also recommend switching to an appropriate oral medication within (b) (4) days of starting Protonix IV, to allow for continued management of the patient's condition (GERD with a history of EE). Although an age-appropriate oral pantoprazole formulation is unavailable for patients <5 years of age, other oral acid suppression therapies are available.

Abbreviation(s): EE, erosive esophagitis; GERD, gastroesophageal reflux disease; IV, intravenous; NERD, nonerosive reflux disease; PK, pharmacokinetic

2.2. Conclusions Regarding Benefit-Risk

GERD is a condition where the reflux of gastric contents into the esophagus results in symptoms and/or complications related to damaged esophageal mucosa from the presence of gastric acid in the esophagus. GERD can present as symptomatic nonerosive GERD (NERD) or EE, a complication and a subtype of GERD characterized by presence of esophageal erosions. PPIs remain the mainstay in the treatment of GERD and EE in pediatric patients. There remains a need for age-appropriate formulations of PPIs, including IV formulations for the management of GERD and EE in pediatric patients.

The Applicant (b) (4) Protonix IV for the treatment (up to 7 days) of GERD associated with a history of EE in pediatric patients (b) (4) and older. To support the proposed indication for Protonix IV in pediatric patients (b) (4) and older for the treatment (up to 7 days) of GERD and a history of EE, the Applicant submitted results from a prospective PK and safety study B1791089 in pediatric patients 1 to 16 years of age, relevant data from legacy trials of oral and IV pantoprazole in pediatric subjects, literature, postmarketing safety database and results from an observational safety study in pediatric patients <2 years old.

Effectiveness of Protonix IV was established through extrapolation of efficacy from adequate and well controlled trials of IV and oral pantoprazole in adults and from clinical trials of oral pantoprazole in pediatric subjects 1 year of age and older with EE, with additional pharmacokinetic data of IV pantoprazole in pediatric subjects 1 year of age and older and oral pantoprazole in pediatric subjects <1 year of age. Study B1791089 demonstrated similar exposure between pediatric subjects 1 year and older following the proposed dosing regimen and adults following the approved dosing regimen. Although the oral pantoprazole PK/pharmacodynamic (PD) relationship (median gastric pH and %Time pH >4) was comparable between infants <1 year of age receiving oral pantoprazole to adults receiving IV/oral pantoprazole, the PK of IV pantoprazole could not be reliably predicted in pediatric patients <3 months of age; extrapolating efficacy of pantoprazole to infants <3 months of age was not supported by the available data. In general, the disease pathogenesis and response to treatment with PPIs are sufficiently similar between adult and pediatric populations with EE. Additionally, pantoprazole is a proton pump inhibitor, a drug class with multiple approved products for which data are available from both adult and pediatric trials that provide for a well understood mechanism of action for treating acid-mediated diseases, including GERD with EE and symptomatic non-erosive GERD, and a well characterized safety profile. Therefore, there is a substantial level of confidence in the available evidence to support relying on extrapolation of efficacy to expand the indication for IV pantoprazole to include treatment of GERD with a history of EE for up to 7 days in pediatric patients 3 months and older. Additionally, studies in neonates (<1 month of age) have been waived due to the rarity of the disease in this age group such that studies are impossible or highly impracticable in this age group.

Safety in the pediatric age groups was supported by data from Study B1791089 in subjects 1 to 16 years of age using IV pantoprazole and legacy studies in pediatric subjects following IV and oral pantoprazole. The dosing regimens evaluated in Study B1791089 were either similar to or higher than the proposed dosing regimens. Therefore, the studied dosing regimens in pediatric subjects 1 year and older across the three body weight cohorts provided adequate exposure coverage to support the safety evaluation for the proposed dosing regimens. Safety data from a

legacy clinical trial of oral pantoprazole in infants <1 year of age with symptomatic GERD (indication not labeled for oral pantoprazole), as well as comparison of safety and systemic exposures from legacy clinical trials of oral and IV pantoprazole in pediatric patients 1 to <2 years of age helped support safety in infants 3 months to <1 year of age. The well-established safety of pantoprazole in adults and older pediatric cohorts overall helped support the safety of IV pantoprazole in infants 3 months to <1 year of age who were not enrolled in Study B1791089. Adequate safety margins for the predicted IV PK in infants have been demonstrated in the juvenile animal studies. Findings from the observational cohort study B1791096 of IV pantoprazole in infants and subjects 1 to <2 years of age provided additional support of safety.

In conclusion, the benefit-risk is favorable for use of Protonix IV for the treatment of GERD and a history of EE for up to 7 days in pediatric patients 3 months and older.

II. Interdisciplinary Assessment

3. Introduction

In this efficacy supplement (NDA 20988/S-070), the Applicant is proposing Protonix IV (pantoprazole sodium) for Injection for "the short-term (up to 7 days) treatment of pediatric patients aged (b) (4) and older with gastroesophageal reflux disease (GERD) and a history of EE," with the following proposed dosing recommendations:

- (b) (4) to less than 1 year of age: 0.8 mg/kg with maximum dose of 10 mg once daily (QD)
- 1 year to 17 years:
  - Body weight (BW) 15 kg or less: 10 mg QD
  - BW greater than 15 kg to 40 kg or less: 20 mg QD
  - BW greater than 40 kg: 40 mg QD

Pantoprazole, a proton pump inhibitor (PPI), acts by suppressing 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 cells, thus leading to the inhibition of both basal and stimulated gastric acid secretion.

GERD is a condition in which the reflux of gastric contents into the esophagus results in symptoms and/or complications. GERD can present as nonerosive reflux disease or erosive esophagitis (EE). Common symptoms of GERD in adults, as well as in older children, include heartburn and regurgitation. Infants and younger children with GERD may exhibit varying symptoms, such as feeding difficulties, poor weight gain, vomiting, choking, and gagging. Alarm symptoms may include dysphagia, odynophagia, anemia, weight loss, hematemesis, or recurrent vomiting. Complications of GERD include esophagitis, esophageal strictures, Barrett's esophagus, and esophageal adenocarcinoma. GERD has an estimated prevalence of 18.1% to 27.8% in North America.[7] A systematic literature review found the prevalence of GERD symptoms in infancy ranged from 23.1% to 40% with a decrease in prevalence as infant age increased. In children younger than 10 years, overall prevalence of weekly GERD symptoms was 3.2%. In children older than 10 years, reported weekly GERD symptom prevalence varied from 0.2% to 18.8%.[8] In pediatric patients, symptoms of GERD can vary depending on the age. A thorough medical history and examination are crucial for an accurate diagnosis and management of GERD. The pathophysiology is multifactorial, with contributing mechanisms including hiatal anatomic changes (i.e., hiatal hernia), lower esophageal sphincter incompetence, esophageal acid exposure, insufficient esophageal motility, delayed gastric emptying, and obesity. The diagnosis may be based on a combination of symptom presentation, endoscopic evaluation of esophageal mucosa, reflux monitoring, and response to therapeutic intervention.

[7] H El-Serag, S Sweet, C Winchester, and J Dent, 2014, Update on the Epidemiology of Gastro-Oesophageal Reflux Disease: A Systematic Review, Gut, 63(6):871–880.

[8] S Bingham and P Muniyappa, 2020, Pediatric Gastroesophageal Reflux Disease in Primary Care: Evaluation and Care Update, Curr Probl Pediatr Adolesc Health Care, 50(5):100784.

The approach to managing GERD is based on symptom presentation and endoscopic findings (e.g., presence of EE). In most patients, the symptoms, and endoscopic signs of acid-mediated esophageal damage resolve with dietary/lifestyle modifications and pharmacologic therapy to reduce or neutralize gastric acid secretion. These medications include PPIs, histamine-2 receptor antagonists, and antacids. Surgical or endoscopic treatment is recommended for patients who have persistent symptoms or develop complications despite medical therapy. In the United States, histamine-2 receptor antagonist drugs famotidine and ranitidine are approved for use in pediatric patients for the treatment of symptomatic nonerosive GERD (or NERD) and/or EE due to GERD down to 1 month of age, while nizatidine oral solution is approved in adolescent patients for the treatment of EE, ulcerative esophagitis, and associated heartburn due to GERD. See Table 4. Oral PPIs including omeprazole, esomeprazole, lansoprazole, dexlansoprazole, and pantoprazole are approved for use in pediatric patients. See Table 5. Available dosage forms include delayed-release (DR) tablets and DR suspension. Proton pump inhibitor drug products differ with respect to their approved pediatric indications (i.e., symptomatic GERD, healing of EE, and/or maintenance of healing of EE) and the age groups approved. Only intravenous (IV) esomeprazole is approved in pediatric patients and is the only PPI approved in patients down to 1 month of age for the short-term treatment of GERD with EE as an alternative to oral therapy. Proton pump inhibitors have not demonstrated efficacy in infants <1 year of age with symptomatic nonerosive GERD and are not approved for this indication.

Table 4. Summary of Approved H2 Receptor Antagonists for Pediatric Use

<table>
<tr><th>Product Name(s)</th><th>H2-Receptor Antagonists
Relevant Pediatric Age Groups, Indications and Dosing Regimen</th></tr>
<tr><td>Famotidine (Pepcid®); Oral
NDA 019462
NDA 019510
NDA 019527
NDA 020572
Initial approval: 1986</td><td>
<table>
<tr><th>Indication</th><th>Pediatric Age Range</th><th>Recommended Dosage[a]</th><th>Duration</th></tr>
<tr><td>Peptic Ulcer Disease</td><td>1 year to less than 17 years</td><td>Starting dosage 0.5 mg/kg once daily; or 0.25 mg/kg twice daily.

May increase to 1 mg/kg once daily at bedtime or 0.5 mg/kg twice daily

Maximum of 40 mg per day</td><td>8 weeks[b]</td></tr>
<tr><td rowspan="2">GERD</td><td>Birth to less than 3 months</td><td>Starting dosage 0.5 mg/kg once daily.
May increase to 1 mg/kg once daily[b]</td><td rowspan="2">Up to 8 weeks[b,c,d]</td></tr>
<tr><td>3 months to less than 1 year</td><td>Starting dosage 0.5 mg/kg twice daily.
May increase to 1 mg/kg twice daily[c]

Maximum of 40 mg per day</td></tr>
<tr><td>GERD with or without esophagitis and ulcerations</td><td>1 year to less than 17 years</td><td>0.5 mg/kg twice daily

Maximum of 40 mg twice daily</td><td>6 to 12 weeks[b]</td></tr>
</table>
</td></tr>
<tr><td>Ranitidine (Zantac®); Oral
NDA 019675
Initial approval: 1988</td><td>Pediatric Use: The safety and effectiveness of ZANTAC have been established in the age-group of 1 month to 16 years. There is insufficient information about the pharmacokinetics of ZANTAC in neonatal patients (less than 1 month of age) to make dosing recommendations.
The following 3 subsections provide dosing information for each of the pediatric indications. Also, see the subsection on Preparation of ZANTAC 25 EFFERdose Tablets, below.
Treatment of Duodenal and Gastric Ulcers: The recommended oral dose for the treatment of active duodenal and gastric ulcers is 2 to 4 mg/kg twice daily to a maximum of 300 mg/day. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients.
Maintenance of Healing of Duodenal and Gastric Ulcers: The recommended oral dose for the maintenance of healing of duodenal and gastric ulcers is 2 to 4 mg/kg once daily to a maximum of 150 mg/day. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients.
Treatment of GERD and Erosive Esophagitis: Although limited data exist for these conditions in pediatric patients, published literature supports a dosage of 5 to 10 mg/kg/day, usually given as 2 divided doses.</td></tr>
</table>

Product Name(s)	H2-Receptor Antagonists Relevant Pediatric Age Groups, Indications and Dosing Regimen
Ranitidine (Zantac®); Injection NDA 19090 Initial approval: 1984	ZANTAC Injection and ZANTAC Injection Premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication. **Pediatric Use:** The safety and effectiveness of ZANTAC Injection have been established in the age-group of 1 month to 16 years for the treatment of duodenal ulcer. Use of ZANTAC in this age-group is supported by adequate and well-controlled studies in adults, as well as additional pharmacokinetic data in pediatric patients, and an analysis of the published literature. **Pediatric Use:** While limited data exist on the administration of IV ranitidine to children, the recommended dose in pediatric patients is for a total daily dose of 2 to 4 mg/kg, to be divided and administered every 6 to 8 hours, up to a maximum of 50 mg given every 6 to 8 hours. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients. Limited data in neonatal patients (less than 1 month of age) receiving ECMO have shown that a dose of 2 mg/kg is usually sufficient to increase gastric pH to >4 for at least 15 hours. Therefore, doses of 2 mg/kg given every 12 to 24 hours or as a continuous infusion should be considered.
Nizatidine (Axid®); Oral NDA 019508 NDA 021494 Initial approval: 1988	*Pediatric Dosing*—Each mL of oral solution contains 15 mg of nizatidine. Axid® Oral Solution is indicated for pediatric patients 12 years of age or older. For pediatric patients 12 years of age and older, the dosage of nizatidine is 150 mg b.i.d. (2 tsp, b.i.d.) The following dosage recommendations are provided: Erosive Esophagitis—For pediatric patients 12 years or older, the dosage is 150 mg b.i.d. (300 mg/d). The maximum daily dose for nizatidine PO is 300 mg/d. The dosing duration may be up to eight weeks. Gastroesophageal Reflux Disease— For pediatric patients 12 years or older, the dosage is 150 mg b.i.d. (300 mg/d). The maximum daily dose for nizatidine PO is 300 mg/d. The dosing duration may be up to eight weeks.

Source: Approved US Prescribing Information for Pepcid (August 15, 2019), Zantac (September 4, 2009), Axid (March 21, 2005) Accessed through Drugs@FDA
Abbreviation(s): b.i.d., twice a day; d, day; ECMO, extracorporeal membrane oxygenation; GERD, gastroesophageal reflux disease; IV, intravenous; PO, by mouth

Table 5. Summary of Approved PPIs for Pediatric Use[9]

PPI	Route	Age	Indication (USPI)	Treatment Duration
Pantoprazole (PROTONIX)[a]	Oral	≥5 y	Healing and symptomatic relief of EE	≤8 weeks
Omeprazole (PRILOSEC)[b]	Oral	≥1 y 1 mo to <1 y ≥1 y ≥1 y	Symptomatic GERD EE due to acid-mediated GERD EE due to acid-mediated GERD which has been endoscopically confirmed EE maintenance of healing	Up to 4 weeks Up to 6 weeks 4-8 weeks Not available
Esomeprazole (NEXIUM) [c, d]	Oral IV	1 to 17 y 1 to 17 y 1 mo to < 1 y 1 mo to 17 y	Healing of EE Symptomatic GERD EE due to acid-mediated GERD GERD with EE	4-8 weeks 4-8 weeks Up to 6 weeks ≤ 10 days (and switch as soon as oral is suitable)
Lansoprazole (PREVACID)[e]	Oral	≥1 y to 11 y 12 to 17 y ≥1 y to 11 y 12 to 17 y	Symptomatic GERD Symptomatic GERD Healing and symptom relief of EE Healing and symptom relief of EE	≤12 weeks ≤8 weeks ≤12 weeks ≤8 weeks

Source: NDA 20988/S-070 Module 2.7.3., Summary of Clinical Efficacy, Table 1
Abbreviation(s): EE, erosive esophagitis; GERD, gastroesophageal reflux disease; IV, intravenous; mo, month; PPI, proton pump inhibitor; USPI, United States prescribing information; y, year(s)

Protonix IV (pantoprazole sodium) for injection is approved in adults for the i) short-term treatment (7 to 10 days) of GERD associated with a history of EE and for ii) pathological hypersecretion conditions, including Zollinger-Ellison Syndrome. It is available as a 40 mg pantoprazole freeze-dried powder in a single-dose vial for reconstitution (NDA 20988). Pantoprazole sodium is also available as DR granules for oral suspension containing 40 mg pantoprazole in a unit-dose packet (NDA 22020) and as 20 mg or 40 mg DR oral tablets (NDA 20987).

Postmarketing requirements (PMRs) were issued under Pediatric Research Equity Act (PREA) at the time of the original Protonix IV NDA approval (2001) and under S-027 (2004) that are addressed with this efficacy supplement:

- 255-6: Deferred pediatric study under PREA for the short-term treatment (7 to 10 days) of GERD as an alternative to oral therapy in patients 2 to 16 years of age who are unable to take Protonix (pantoprazole sodium) DR tablets *[Issued March 22, 2001]*
- 145-1: Deferred pediatric study under PREA for the treatment of GERD in pediatric patients ages 0 to 16 *[Issued on December 6, 2004]*

[9] The safety and effectiveness of Protonix for short-term treatment (up to eight weeks) of EE associated with GERD have been established in pediatric patients 1 year through 16 years of age. For patients less than 5 years of age, there is no appropriate dosage strength in an age-appropriate formulation available. Therefore, Protonix is indicated for the short-term treatment of EE associated with GERD for patients 5 years and older.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Adequacy of Available Data to Support Use in Infants <1 Year of Age

3.1.2. Key Safety Review Issues

3.1.2.1. Safety in Infants 1 to 11 Months of Age

3.1.2.2. Safety in Pediatric Patients With EE

3.2. Approach to the Clinical Review

As previously noted, new efficacy data with IV pantoprazole were not provided in this submission. Use of Protonix IV in pediatric patients is based on extrapolation of efficacy data from clinical trials in adults (oral and IV) and pediatric subjects 1 year of age and older (oral)[3], and dose selection is based on exposure matching of pantoprazole between adults and pediatric populations. Therefore, the review team assessed whether the available PK data support a reliable estimation of pantoprazole exposures in pediatric patients and dose selection for IV pantoprazole across the proposed age range of (b) (4) to 16 years of age. The review team evaluated the available PK data from Study B1791089 in pediatric patients 1 to 16 years of age, the population pharmacokinetics (PopPK) model to support the exposure comparison between pediatric subjects 1 month to 16 years of age following the proposed dosing regimen and adults following the approved dosing regimen, as well as PK data from legacy Wyeth studies conducted in pediatric subjects birth to at least 16 years of age (previously submitted and reviewed under NDA 22020 for oral and IV pantoprazole). See Section 14.

The team's assessment of safety involved evaluating the adequacy of safety data to support an indication for Protonix IV in pediatric patients with GERD and a history of EE. This was achieved through a review of new safety information from Study B1791089 following single and multiple doses (4 to 7 days) of IV pantoprazole in pediatric subjects 1 to 16 years of age with GERD, safety from legacy studies (oral and IV) in pediatric subjects 1 month of age and older, and the findings from the retrospective observational cohort study B1791096. Safety from the 4-month safety update, published literature, and postmarketing safety database (reviewed in conjunction with the Division of Pharmacovigilance-I) were incorporated in the clinical review approach for safety.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):

   For treatment of gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE) for up to 7 days in pediatric patients 3 months and older.

2. Substantial evidence of effectiveness (SEE) was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*

   a. Adequate and well-controlled (AWC) clinical investigation(s):

      i. ☐ Two or more AWC clinical investigations, **OR**

      ii. ☐ One AWC clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☐ One AWC clinical investigation and confirmatory evidence[10,11,12]

      OR

   c. ☒ Evidence that supported SEE from a prior approval (extrapolation)[2]

3. Complete response, if applicable

   a. ☐ SEE was established

   b. ☐ SEE was not established *(if checked, omit item 2)*

[10] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) (https://www.fda.gov/media/133660/download). When final, this guidance will represent the FDA's current thinking on this topic.

[11] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (May 1998) (https://www.fda.gov/media/71655/download).

[12] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023) (https://www.fda.gov/media/172166/download). When final, this guidance will represent the FDA's current thinking on this topic.

Table 6. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Protonix IV

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Enrolled	Number of Centers and Countries
B1791089 (02401035)	Hospitalized pediatric subjects 1 to 16 years of age who are candidates for acid suppression therapy	Control type: Uncontrolled Randomization: 19 enrolled Blinding: N/A; Open label Biomarkers: N/A Innovative design features: N/A	Drug: Protonix IV (pantoprazole sodium) Dosage: 10 mg (for BW <15 kg), 20 mg (for BW ≥15 kg to <40 kg), and 40 mg (for BW ≥40 kg) Number treated: N=18 Duration (quantity and units): 4 to 7 days	Primary: PK (CL, V_d) Secondary: PK (C_{max}, AUC), safety, tolerability	24 planned (12 per age cohort: 1-<2 years and 2-16 years); 19 enrolled 18 completed	26 centers in 6 countries participated; 8 centers enrolled patients.

Source: Reviewer's Table.
[1] Includes all submitted interventional clinical trials.
Abbreviation(s): AUC, area under the concentration-time curve; BW, body weight; CL, clearance; C_{max}, peak serum drug concentration; d, day; IV, intravenous; N, number of subjects; N/A, not applicable; NCT, national clinical trial; PK, pharmacokinetic; V_d, volume of distribution

Additionally, the Applicant submitted results from "A Real-World Study Evaluating the Safety of Pantoprazole Sodium Intravenous in Infants Aged 1 Month to <1 Year and Patients Aged 1 to <2 Years Using an Electronic Health Records Database from the United States (B1791096)." Safety data were included from 3476 eligible subjects (1 month to <2 years) identified through electronic health records (EHR). The study assessed 25 prespecified safety outcomes of interest (SOI) in infants 1 to 11 months of age, and pediatric patients 1 to <2 years of age who had received at least one dose during the 90 days evaluation period. The primary objective was to estimate incidence for 25 SOIs in infants with GERD grouped by age (1 month to <1 year and 1 to <2 years), and the secondary objective was to estimate the incidence for 25 SOIs in infants without GERD grouped by age and to identify (in infants with GERD) diagnostic codes frequently documented in temporal proximity to IV pantoprazole administrations. See Section 15.2.

4. Patient Experience Data

Not applicable.

Table 7. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

No new nonclinical studies assessing the effectiveness of pantoprazole have been submitted in this supplement and the Applicant cross-referenced NDA 22020 and NDA 20988 initial submission. The nonclinical effectiveness of pantoprazole for the treatment of gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis (EE) was reviewed in the previous marketing applications (NDA 20987, NDA 22020 and NDA 20988).

5.2. Clinical Pharmacology/Pharmacokinetics

The current supplement NDA 20988/S-070 characterized PK in pediatric subjects 1 month to 16 years old following IV administration of pantoprazole.

Table 8. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Proton-pump inhibitor
Mechanism of action	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.
Active moieties	Pantoprazole
QT prolongation	(Not available)
	General Information
Bioanalysis	Pantoprazole plasma concentration were measured in pediatric subjects in Study B1791089 using a validated HPLC-MS/MS method
Healthy subjects versus patients	No differences in systemic exposure were observed between healthy subjects and subjects with EE. See Table 21.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	See Section 6.1
Range of effective dose(s) or exposure	40 mg intravenous administration once daily for 7 to 10 days in adults
Dose proportionality	Pantoprazole peak serum concentration (C_{max}) and area under the serum concentration-time curve (AUC) increase in a manner proportional to intravenous doses from 10 mg to 80 mg.
Accumulation	Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing.
Time to achieve steady-state	Not applicable
Bridge between to-be-marketed and clinical trial/study formulations	Final formulation (pantoprazole sodium for injection, for intravenous use) was used in the PK studies to characterize pantoprazole PK in children 1 to <17 years old.

Characteristic	Drug Information
	Distribution
Volume of distribution	Approximately 11 to 23.6 L
Plasma protein binding	98%, primarily to albumin
Drug as substrate of transporters	(Not available)
	Elimination
Mass balance results	After administration of a single intravenous dose of ^{14}C-labeled pantoprazole sodium to healthy, extensive CYP2C19 metabolizers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.
Clearance	7.6 to 14 L/h.
Half-life	Approximately one hour
Metabolic pathway(s)	The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4.
	Intrinsic Factors and Specific Populations
Body weight	Body weight is the most significant intrinsic factors that correlated with pantoprazole clearance and exposure
Age	Age dependent clearance after adjusting for bodyweight effect on pantoprazole clearance played a major role in neonates and infants <1 year old. After repeated intravenous administration in elderly subjects (65 to 76 years of age), the AUC and elimination half-life values of pantoprazole were similar to those observed in younger subjects.
Renal impairment	In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects.
Hepatic impairment	In patients with mild to severe hepatic impairment (Child-Pugh Class A to C), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects when pantoprazole sodium was administered orally. Although serum half-life values increased to 7 to 9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in CYP2C19 poor metabolizers.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	Clopidogrel is metabolized to its active metabolite in part by CYP2C19. In a crossover clinical study, 66 healthy subjects were administered clopidogrel (300 mg loading dose followed by 75 mg per day) alone and with oral pantoprazole (80 mg at the same time as clopidogrel) for 5 days. On Day 5, the mean AUC of the active metabolite of clopidogrel was reduced by approximately 14% (geometric mean ratio was 86%, with 90% CI of 79 to 93%) when pantoprazole sodium was co-administered with clopidogrel as compared to clopidogrel administered alone.
Inhibition/induction of transporter systems	(Not available)

Source: Reviewer generated
Abbreviation(s): PK, pharmacokinetic; PPI, proton pump inhibitor

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

Protonix IV was approved in adults for the short-term treatment (7 to 10 days) of GERD associated with a history of EE on March 22, 2001. The approved dosing regimen is 40 mg given QD by IV infusion for 7 to 10 days. Study 3001K1-309-US was conducted in adult subjects with GERD and a history of EE. Gastric acid secretion was stimulated by subcutaneous administration of maximally stimulating doses of pentagastrin (6 µg/kg/h). Equivalence on inhibition of acid output on the last day of 40 mg Protonix IV to the last day of oral Protonix (40 mg; the dose found to be safe and effective for healing of EE and resolution of symptoms associated with GERD) was established.

In support of this efficacy supplement, the Applicant conducted an open-label, multicenter study to evaluate the PK of single and multiple IV doses (4 to 7 days) of pantoprazole in two age cohorts of hospitalized pediatric subjects 1 to 16 years of age who were candidates for acid suppression therapy. Observed PK of pediatric subjects 1 to 16 years of age in Study B1791089 was comparable to adults to inform dose selection and support extrapolation of efficacy in this age group. See Table 15 in Section 14.2.

Along with the previously conducted legacy studies in pediatric subjects from birth to ≤16 years of age following either IV or oral administration of pantoprazole, the Applicant developed a population pharmacokinetics (PopPK) model to support the exposure comparison between pediatric subjects 1 month to 16 years of age following the proposed dosing regimen and adults following the approved dosing regimen. In pediatric subjects 3 months to 16 years of age, the observed PK data and PopPK model reliably characterized PK of IV pantoprazole; however, in pediatric subjects 1 month to <3 months of age, the characterization of IV pantoprazole PK relied on oral pantoprazole PK data and assumptions of bioavailability that cannot be validated. Therefore, the IV PK in pediatric subjects 1 month to <3 months of age cannot be characterized, and efficacy of pantoprazole cannot be extrapolated in the 1 month to <3 months age group.

The PopPK model simulated AUC and C_{max} in pediatric subjects are listed in Table 9 below. Both AUC and C_{max} in each age and bodyweight (BW) cohort were comparable to the observed data in adults and supported efficacy extrapolation from adult data to the pediatric population.

Table 9. Drug Exposure at Steady State Following Protonix IV Dosing

Age	Body Weight	Dose	AUC (µg.h/mL)	C_{max} (µg/mL)
3 months to <1 year old		0.8 mg/kg (not to exceed 10 mg)	5.0±3.4	6.3±3.2
1 to 2 years old	8 to <15 kg	10 mg	5.3±5.3	5.1±2.3
	15 to <40 kg	20 mg	8.7±5.7	7.7±2.8
2 years old and older	8 to <15 kg	10 mg	4.9±3.6	4.6±2.0
	15 to <40 kg	20 mg	6.2±4.6	5.2±2.7
	40 kg and above	40 mg	6.7±4.6	4.7±2.0
Adults		40 mg	6.02±4.18	6.26±3.01

Source: Adapted from Table 21 and Table 24
Abbreviation(s): AUC, area under the concentration-time curve; C_{max}, peak serum drug concentration

Additionally, the comparison of PK/ PD relationship of median 24-hour intragastric pH and % time pH >4.0 between the adults receiving oral/IV pantoprazole and infants <1 year old receiving oral pantoprazole showed a similar PK/PD relationship.

Dosing Regimen

The Applicant proposed the following pediatric dosing regimen.

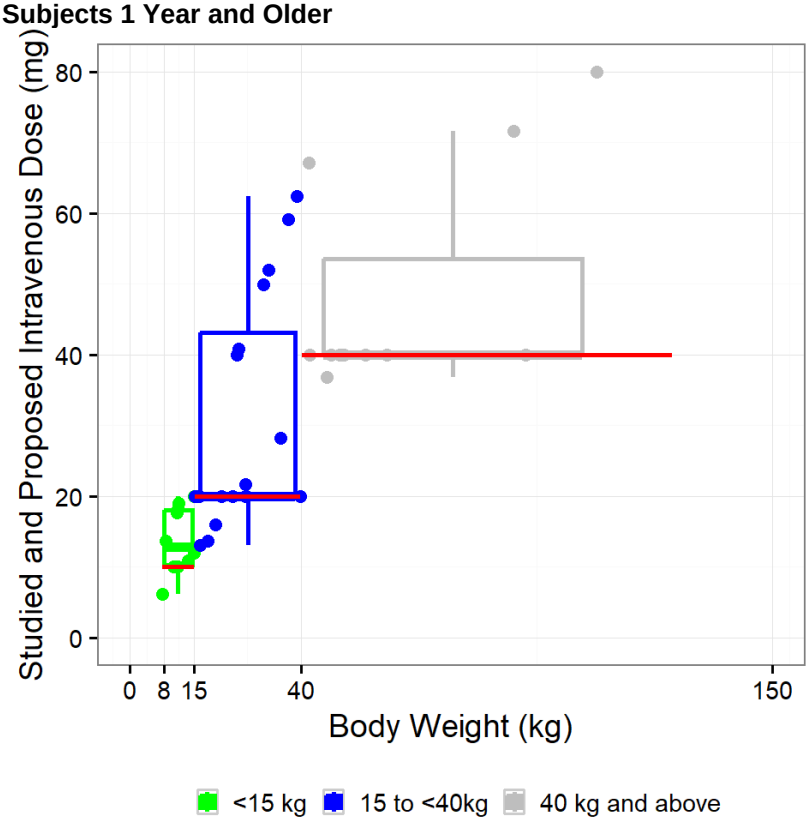
Table 10. Applicant-Proposed Pediatric Dosing Regimen

Age	Body Weight	Dosage Regimen
(b) (4) to <1 year of age		0.8 mg/kg once daily [Not to exceed 10 mg]
(b) (4) of age	≤15 kg	10 mg once daily
	>15 kg to ≤40 kg	20 mg once daily
	>40 kg	40 mg once daily

Source: Applicant proposed USPI.

Of note, the proposed dosing regimen was slightly different from the studied dosing regimen in Study B1791089 in terms of BW cutoff values. In Study B1791089, pediatric subjects 1 year and older with BW <15 kg (instead of ≤15 kg) taking 10 mg pantoprazole QD, ≥15 kg to <40 kg (instead of >15 kg to ≤40 kg) taking 20 mg pantoprazole QD, and ≥40 kg (instead >40 kg) taking 40 mg pantoprazole QD were studied. A comparison of studied IV dosing regimen in all relevant pediatric studies and the proposed dosing regimen are given in Figure 1. For details regards to dose selection, see Section 14.

Figure 1. Comparison Between Studied and Proposed Intravenous Dosing Regimens in Pediatric Subjects 1 Year and Older



Source: Figure 5 in Section 14 Clinical Pharmacology
Solid dots: Studied dosing regimens
Boxplot: Studied dosing regimens
Red horizontal line: The Applicant-proposed dosing regimens

Notwithstanding the slightly different BW cutoff values, the proposed dosing regimen is acceptable taking consideration of the following:

1. The proposed dosing regimen is supported by PK simulation and exposure matching.
2. The slightly different BW cutoff values had impact only for pediatric subjects with an exact BW of 15 kg and 40 kg. The overall exposure in each BW cohort remains similar.

Based on the available data, the review team recommends the following dosing regimen for labeling.

Table 11. Recommended Pediatric Dosage Regimen for GERD and a History of EE

Age	Body Weight	Dosage Regimen (up to 7 Days)
3 months to less than 1 year of age	Less than 12.5 kg	0.8 mg/kg once daily
	12.5 kg and above	10 mg once daily
1 year to 17 years of age	Up to 15 kg	10 mg once daily
	Greater than 15 kg up to 40 kg	20 mg once daily
	Greater than 40 kg	40 mg once daily

Source: Reviewer generated adapted from the recommendations in the prescribing information
Abbreviation(s): EE, erosive esophagitis; GERD, gastroesophageal reflux disease

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

Efficacy trials were not conducted for this pediatric supplement for Protonix IV. Use of Protonix IV in pediatric patients 3 months and older relies on extrapolation of efficacy from adequate and well controlled studies that supported approval of IV and oral pantoprazole sodium in adults and oral pantoprazole in pediatric subjects,[3] with additional PK (see Section 14.5) and safety data of IV pantoprazole in pediatric patients 1 to 16 years of age (see Section 7.6) and legacy oral and IV studies in pediatric patients including infants <1 year of age (see Sections 7.6 and 17).

6.3. Key Efficacy Review Issues

6.3.1. Adequacy of Available Data to Support Use in Infants <1 Year of Age

Issue

Efficacy data were available from adequate and well-controlled studies of intravenous and oral pantoprazole in adults and oral pantoprazole in pediatric subjects 1 year of age and older. Observed PK of pediatric subjects 1 to 16 years of age in Study B1791089 was comparable to adults to inform dose selection and support extrapolation of efficacy in this age group. See Section 14.2. Infants <1 year of age were not enrolled in Study B1791089. Efficacy and PK data were unavailable in pediatric subjects <1 year of age. The Applicant developed a population pharmacokinetics (PopPK) model to support the exposure comparison between pediatric subjects 1 month to 16 years of age following the proposed dosing regimen and adults following the approved dosing regimen. The review team considered the adequacy of the available data to support relying on extrapolation of efficacy from adequate and well controlled trials in adults and older pediatric subjects at least 1 year of age to infants 1 month to <1 year of age.

Background

The proposed use (up to 7 days) of Protonix IV in pediatric patients includes infants, (b) (4) 11 months of age. As previously noted, an extrapolation of efficacy approach was proposed by the Applicant, with dose selection using exposure matching of pantoprazole between pediatrics and adults. Per the draft guidance for industry *Pediatric Gastroesophageal Reflux Disease: Developing Drugs for Treatment* (October 2017),[13] extrapolation of efficacy from adult populations to pediatric populations may be appropriate if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients. Extrapolation of efficacy from one pediatric age group to another pediatric age group also may be appropriate. Furthermore, the Gastrointestinal Advisory Committee meeting in 2010 noted that extrapolation to adult disease can be accepted in infants 1 month to 11 months of age for acid-mediated

[13] See the draft guidance for industry *Pediatric Gastroesophageal Reflux Disease: Developing Drugs for Treatment* (October 2017) (https://www.fda.gov/media/108594/download). When final, this guidance will represent the FDA's current thinking on this topic.

conditions such as EE and supported reliance on PK/PD and safety studies of PPIs.[14] These recommendations did not apply to premature infants and neonates. Additionally, pantoprazole is a proton pump inhibitor, a drug class with multiple approved products for which data are available from both adult and pediatric trials that provide for a well understood mechanism of action for treating acid-mediated diseases, and well characterized associated safety profile. Therefore, there is a substantial level of confidence in the available evidence to support relying on extrapolation of efficacy. The review team determined that extrapolation of efficacy from adults to pediatric patients with GERD with a history of EE was generally acceptable and aligned with the approach taken in other similar indications for this drug class; (b) (4) .

While Study B1791089 provided PK data following IV pantoprazole in pediatric patients 1 year and older, infants were not enrolled into this study and therefore PK data following an IV route were unavailable in this age group for exposure matching and dose selection. In lieu of a PK study, the Applicant proposed to utilize PK modeling and simulation approach for exposure-matching and dose selection in this age group. The Applicant relied on oral administration PK data in infants <1 year old and on both IV and oral administration PK data in pediatric subjects 1 year and older to support the exposure assessment of IV pantoprazole PK in infants 1 to <1 year of age.

Assessment

To support pediatric extrapolation, the Applicant developed a PopPK model of pantoprazole using the IV PK data characterized in Study B1791089 in pediatric subjects 1 to 16 years of age and PK information from legacy studies of oral and IV pantoprazole in pediatric subjects from birth to 16 years of age. The Applicant compared pantoprazole exposure-response relationships following single and multiple dosing in neonates, infants, and adults. Figure 12 and Figure 13 present the median 24-hour intragastric pH versus oral pantoprazole exposure (AUC) and % time intragastric pH above 4 versus oral pantoprazole exposure (AUC), respectively, following multiple doses (once daily dosing for 5 to 7 days) in neonates, infants, and adults. The exposure-response relationships (median 24-hour intragastric pH and % time pH >4.0) of oral pantoprazole are reasonably overlapping between the adult and infants <1 year old. See Section 14.5. These data supported the efficacy extrapolation from adults to infants <1 year old with GERD associated with EE.

While the PK/PD comparison between infants <1 year of age receiving oral pantoprazole and adults receiving oral/IV pantoprazole support extrapolation of efficacy to infants <1 year of age with EE, the PK of Protonix IV could be reliably characterized only down to 3 months of age to support dose selection by exposure matching. The PK of IV pantoprazole in infants 1 month to <1 year of age was estimated based on PK data with oral pantoprazole, with the assumption that the bioavailability is the same between infants 1 month to <1 year of age and pediatric subjects 1 to 6 years old. The review team's analysis suggested that area under the concentration-time curve (AUC) following oral administration was age-dependent in infants <3 months old after dose and BW adjustment (Figure 7), and whether bioavailability in infants <3 months is consistent with

[14] FDA, 2010 Meeting Materials, Gastrointestinal Drugs Advisory Committee, accessed May 21, 2024, https://web.archive.org/web/20170111202447/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm195280.htm.

older pediatric subjects remained unclear. Therefore, the PK of IV pantoprazole could not be predicted reliably in infants 1 to <3 months of age [redacted] (b) (4)

Conclusion

The available data support extrapolation of efficacy for Protonix IV for infants 3 to 11 months of age.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No new nonclinical study reports have been submitted in this supplement. Toxicology studies in juvenile animals with pantoprazole sodium were reviewed previously under the different submission (IND 35441, IND 52132, IND 68011 and NDA 22020/S001, NDA 22020/S002, NDA 20987/S036 and NDA 20987/S037). Key findings are summarized below.

In juvenile animal studies, pantoprazole was administered to neonatal rats (4 weeks) and dogs (13 weeks) beginning on postnatal day 4 and day 1, respectively. Stomach was the common target organ of toxicity and mucosal alterations in the stomach were observed in both rats and dogs. In rats, eosinophilic chief cells were observed in the fundic mucosa of male and female pups in all treatment groups, and the changes were reversed after a 90-day recovery period. In dogs, changes in the stomach included increased mucosal height, infiltration of mononuclear cells, glandular necrosis, hypertrophy of parietal cells, atrophy of chief cells, and glandular dilation. The changes were not reversed completely at the end of the 13-week recovery period. In dog pups, increased cholesterol and triglyceride levels were observed at 10 and 30 mg/kg/day and were reversed at the end of the 13-week recovery period. Decreased hemoglobin and hematocrit values were observed in both species. Similar findings, except glandular necrosis in the stomach, were also observed in adult rats and dogs. There were no effects on the development of physical landmarks or overall growth in neonatal/juvenile rats or dogs.

In a 15-day IV toxicity study in juvenile rats, groups of animals received pantoprazole at IV doses of 0, 3, 10 and 30 mg/kg/day from postnatal day (PND) 14 through 28. The incidence of eosinophilic chief cells in the glandular stomach was higher in all treatment groups than in controls. The incidence was higher in female pups than in males. Male pups receiving the high dose had higher incidences of extramedullary hematopoiesis in the liver and lymphohistiocytic inflammation of the prostate. The target organs of toxicity were the stomach, liver, and prostate. The tolerated dose was the maximum tested dose of 30 mg/kg/day in this study, with corresponding maximum plasma concentration (C_{max}) and area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) values of 39.35 µg/mL and 28.65 µg.h/mL, respectively, on PND 28. The C_{max} in juvenile rats at the tolerated dose is 11.2-fold and 9.2-fold higher than the predicted C_{max} in 1 to <2 months and 11 to <12 months old infants, respectively, at the proposed IV dose of 0.8 mg/kg. The exposures (AUC) in juvenile rats at the tolerated dose

were 5.1-fold and 7.1-fold higher than the predicted exposures (AUC) in 1 to <2 months and 11 to <12 months old infants, respectively, at the proposed IV dose of 0.8 mg/kg. The C_{max} and AUC in juvenile dogs at the 30 mg/kg dose provide almost similar exposure margins for the 2 to <11 months old pediatric patients (C_{max}: 8.9- to 11.5-fold and AUC: 6.4- to 7.2-fold).

In a separate toxicokinetic study in neonatal/juvenile dogs, the animals were administered oral pantoprazole at dose levels of 3, 10, and 30 mg/kg/day for 7 days. At the 3 mg/kg/day (tolerated dose in the 13-week study) dose, the C_{max} and AUC_{0-24} values were 3.4 μg/mL and 6.4 μg.h/mL, respectively, in this study. The C_{max} in juvenile dogs at the 3 mg/kg dose was 1.0-fold and 0.8-fold higher than the predicted C_{max} in infants 1 to <2 months and 11 to <12 months old, respectively, at the proposed IV dose of 0.8 mg/kg. The exposure (AUC) in juvenile dogs at the 3 mg/kg dose was 1.1-fold and 1.6-fold higher than the predicted exposures (AUC) in infants 1 to <2 months and 11 to <12 months old, respectively, at the proposed IV dose of 0.8 mg/kg. The C_{max} and AUC in juvenile dogs at the 3 mg/kg dose provide almost similar exposure margins for the 2- to <11-month-old pediatric patients (C_{max}: 0.8- to 1.0-fold and AUC: 1.4- to 1.6-fold).

Overall, the toxicological profiles for pantoprazole in neonatal/juvenile rats and dogs were similar to those seen in adult animals and the exposures in neonatal/juvenile animals provide reasonable margins of safety for the proposed pediatric age groups.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Proton pump inhibitors as a class have a well-established safety profile in adults as well as in pediatric patients with acid-mediated conditions. Warnings and precautions associated with pantoprazole and PPIs as a class include acute tubulointerstitial nephritis, fundic gland polyps, hypomagnesemia and mineral metabolism, *Clostridium difficile*-associated diarrhea especially in hospitalized patients, cutaneous or systemic lupus erythematosus, osteoporosis-related fractures of the hip, wrist, or spine, severe cutaneous adverse reactions such as erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis, and vitamin B12 deficiency. Symptomatic response with PPIs also does not preclude the presence of gastric malignancy, and additional testing, including endoscopy, may be required in those with suboptimal response or an early relapse with PPIs. Certain adverse reactions have been linked to high-dose, multiple daily dose, and long-term PPI therapy. Proton pump inhibitors should be used at the lowest dose and shortest duration of therapy appropriate to the condition being treated. Additionally, Protonix IV use has been associated with thrombophlebitis and a potential for exacerbation of zinc deficiency due to the presence of edetate disodium (the salt form of ethylenediaminetetraacetic acid) in the product.

Most common adverse reactions (>2%) in clinical trials of Protonix in adults included headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia. In pediatric trials, most common adverse reactions (>4%) included upper respiratory tract infections (URI), headache, fever, diarrhea, vomiting, rash, and abdominal pain. In a trial in infants with symptomatic GERD, the adverse reactions that were reported more commonly (difference of ≥4%) in the treated population compared to the placebo population were elevated creatine kinase, otitis media, rhinitis, and laryngitis.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

7.3.1. Adverse Events Identified in Postmarket Experiences

Based on a search of the FDA Adverse Event Reporting System and published literature, the Applicant concluded that the overall safety of IV pantoprazole in pediatric patients appears to be consistent with the safety profile in adults. FDA review similarly did not identify any cases indicative of new safety issues in pediatric patients or cases of zinc deficiency, thrombophlebitis, or hepatotoxicity describing new features of these labeled adverse events (AE). Refer to the final consult review by the Division of Pharmacovigilance-I in DARRTs dated April 12, 2024.

7.3.2. Expectations on Safety

Based on the absence of new safety signals during the review of this application and available safety data from the postmarket setting, it is anticipated that the safety of Protonix IV in the postmarket setting will be similar to that generally known for pantoprazole and the PPI class.

7.3.3. Additional Safety Issues From Other Disciplines

Not applicable.

7.4. FDA Approach to the Safety Review

To support the proposed pediatric indication and dosing regimen, safety data from the following sources were reviewed:

1. Study B1791089: An open-label, single-arm, uncontrolled, multicenter study to evaluate PK of single and multiple IV doses of pantoprazole in two age cohorts of hospitalized pediatric subjects 1 to 16 years of age who are candidates for acid suppression therapy [NCT02401035].

   Refer to Section 15.1 for details of the study design.

   The clinical safety review assessed the AEs, clinical laboratory data (hematology, serum chemistry, and urinalysis), vital signs, and physical examinations in subjects following IV pantoprazole once-daily dosing for 4 to 7 days.

2. Relevant safety information from legacy Wyeth studies in pediatric subjects including infants (previously reviewed under NDA 22020 sequence #020 for oral pantoprazole) was assessed. Given these studies were previously reviewed and deemed acceptable under NDA 22020/20987 (clinical review dated August 10, 2009), a detailed review of the findings was not undertaken, but relevant safety findings were summarized as needed to support safety in infants.

3. Relevant safety information from published literature, postmarketing safety database, and the 120-day safety update were also assessed. The safety update (submitted February 27, 2024) included literature and postmarketing safety database findings from the previous cutoff date on May 21, 2023, through January 16, 2024. No new safety signals were identified from this safety update.
4. Study B1791096: A real world study evaluating the safety of pantoprazole sodium IV in infants aged 1 month to <1 year and patients aged 1 to <2 years using an electronic health record database from the United States.

   The incidence rates of 25 prespecified SOIs that were assessed in this study were reviewed, as well as any differential outcomes across age cohorts, disease subgroups, and duration of use of IV pantoprazole.

   Division of Epidemiology (DEPI) review dated February 15, 2024, of the final clinical study report identified three major study limitations: (1) no control group, (2) no information on IV pantoprazole dosing, and (3) weak or empty method for detecting unanticipated AEs. Refer to Section 15.2 for details of the study design.

7.5. Adequacy of the Clinical Safety Database

The supplemental NDA included data from a single-arm, multicenter, PK and safety study in 18 pediatric patients. Study B1791089 assessed the safety and tolerability of IV pantoprazole QD for up to 7 days for a short-term use in subjects with GERD 1 to 16 years of age (n=18) across two age cohorts: Cohort 1 (1 to <2 years, n=2), and Cohort 2 (2 to 6 years; n=16). Across the two age cohorts, the median (min, max) age was 1 (1, 1) and 9 (3, 16), respectively. Subjects received fixed total daily doses of IV pantoprazole based on their weight as follows: BW <15 kg: 10 mg, BW ≥15 kg to <40 kg: 20 mg, and BW ≥40 kg: 40 mg doses. The mean duration of exposure across the two age cohorts was 4 days and 4.9 days, respectively. No subject on the study received less than four doses of once-daily IV pantoprazole.

Table 12. Duration of Exposure, Safety Population, Study B1791089

Parameter	Cohort 1 (1 to <2 Years) N=2	Cohort 2 (2 to 16 Years) N=16	Total N=18
Duration of treatment, days			
Mean (SD)	4 (0)	4.9 (1.4)	4.8 (1.4)
Median (Q1, Q3)	4 (4, 4)	4 (4, 7)	4 (4, 6.2)
Min, max	4, 4	4, 7	4, 7
Subjects treated, by duration, n (%)			
4 days	2 (100)	11 (68.8)	13 (72.2)
7 days	0	5 (31.2)	5 (27.8)

Source: Adapted from CDS-generated Table; adex.xpt and adsl.xpt; Software: R and JMP 16
Duration is 4 to 7 days.
Abbreviation(s): N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Study B1791089 did not enroll infants (1 to 11 months) and had a limited enrollment of subjects 1 to <2 years of age due to enrollment challenges. Therefore, safety data from legacy studies

using IV or oral pantoprazole in pediatric subjects which included patients from these age groups (subjects down to 1 month of age) were also considered.

Pharmacokinetic/exposure comparisons were utilized to justify reliance on safety from legacy studies and/or older pediatric age cohorts or adults as needed. Only one subject with GERD in Study B1791089 was determined to also have EE. Erosive esophagitis is an esophageal complication of GERD and is considered a subtype of GERD The safety of IV pantoprazole is not anticipated to be impacted by disease severity and is more likely to be a function of drug dose, regimen, and duration of use. Given an adequate understanding of the safety of pantoprazole and the drug class in general, as well as the safety of Protonix IV in adults, the review team does not expect the safety profile to differ in pediatric patients for the proposed use of Protonix IV for up to 7 days.

Additionally, findings from the retrospective observational cohort study, B1791096, were also considered to provide additional safety information in infants and pediatric patients 1 to <2 years of age. See Section 15. While the observational study did not constitute a primary support for safety in infants due to study design limitations, it nevertheless provided safety data in these younger subjects that are otherwise difficult to enroll.

Overall, given the collective evidence, the pediatric extrapolation approach including dose-selection based on exposure matching between adults and pediatrics, the available clinical safety database was deemed generally reasonable to address the safety of a short-term use of Protonix IV in the proposed pediatric population with GERD and a history of EE.

7.6. Safety Results

7.6.1. Safety Results, Study B1791089

Table 13 below provides the overview of TEAEs from Study B1791089, an open-label, PK, and safety study of IV pantoprazole in hospitalized pediatric patients 1 to 16 years of age who were candidates for acid suppression therapy. Subjects received fixed daily doses for 4 to 7 days based on their BW.

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Study B1791089

Table 13. Overview of Treatment-Emergent Adverse Events,[1] Safety Population, Study B1791089[2]

Event Category	Cohort 1 (1 to <2 Years) N=2 n (%)	Cohort 2 (2 to 16 Years) N=16 n (%)	Total N=18 n (%)
SAE	0	1 (6.2)	1 (5.6)
SAEs with fatal outcome	0	0	0
Life-threatening SAEs	0	0	0
AE leading to permanent discontinuation of study drug	0	0	0

Event Category	Cohort 1 (1 to <2 Years) N=2 n (%)	Cohort 2 (2 to 16 Years) N=16 n (%)	Total N=18 n (%)
AE leading to dose modification of study drug	0	0	0
AE leading to interruption of study drug	0	0	0
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0
Any AE	0	8 (50.0)	8 (44.4)
Severe and worse	0	0	0
Moderate	0	2 (12.5)	2 (11.1)
Mild	0	6 (37.5)	6 (33.3)

Source: CDS-generated (Salman Hosain, PhD); adae.xpt; Software: R
[1] Treatment-emergent adverse events defined as all AEs that start on or after the first dosing day and time/start time.
[2] Duration is 4 to 7 days.
Severity as assessed by the investigator.
Abbreviation(s): AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

No treatment-emergent adverse events (TEAEs) were noted in Cohort 1 (1 to <2 years). Fifty percent of subjects in Cohort 2 (2 to 16 years) experienced TEAEs during the study. There was one serious adverse event (SAE) in this age group. Most TEAEs were mild, with two subjects experiencing AEs of moderate severity. No subject discontinued due to AEs.

7.6.1.2. Deaths, Study B1791089

No deaths occurred on this study.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Study B1791089

One subject in Cohort 2 (ID (b) (6)) had an SAE of rotavirus infection, which resulted in prolonged hospitalization. The subject was an 8-year-old male with a primary diagnosis of GERD and received IV pantoprazole 20 mg QD for 4 days. On day 4, the subject experienced a TEAE of mild gastroenteritis and an SAE of rotavirus infection that was confirmed through stool analysis. The subject was treated for the TEAE of gastroenteritis, which was resolved on study day 5. The SAE of rotavirus infection resolved on study day 7. The event appears unrelated to the study drug.

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Study B1791089

There were no AEs that led to treatment discontinuation in this study.

7.6.1.5. Treatment-Emergent Adverse Events, Study B1791089

A total of 31 unique TEAEs were observed in 8 of the 18 (44.4%) study subjects following treatment with IV pantoprazole for 4 to 7 days. The age range in subjects experiencing TEAEs was 4 to 15 years. No TEAEs were reported in the two subjects within Cohort 1 (1 to <2 years of

age). Most frequently reported TEAEs included abdominal pain (22%), arthropod bite (11%), headache (11%), pain in extremity (11%), and vomiting (11%). Gastrointestinal disorders, followed by general disorders and administration site conditions, constituted the two most common system organ classes of TEAEs. Overall, the safety profile of IV pantoprazole in pediatric subjects with GERD was comparable to that known in adults and older pediatric patients following IV and/or oral formulations of pantoprazole.

Table 14. Subjects With Treatment-Emergent Adverse Events[1] Preferred Term, Safety Population, Study B1791089[2]

Preferred Term	Cohort 1 (1 to <2 Years) N=2 n (%)	Cohort 2 (2 to 16 Years) N=16 n (%)	Total N=18 n (%)
Any TEAE	0	8 (50%)	8 (44.4%)
Abdominal pain	0	4 (25%)	4 (22.2%)
Headache	0	2 (12.5%)	2 (11.1%)
Pain in extremity	0	2 (12.5%)	2 (11.1%)
Vomiting	0	2 (12.5%)	2 (11.1%)
Arthropod bite	0	2 (12.5%)	2 (11.1%)
Adenoidal hypertrophy	0	1 (6.2%)	1 (5.6%)
Aphthous ulcer	0	1 (6.2%)	1 (5.6%)
Back pain	0	1 (6.2%)	1 (5.6%)
Blister	0	1 (6.2%)	1 (5.6%)
Catheter site erythema	0	1 (6.2%)	1 (5.6%)
Catheter site pain	0	1 (6.2%)	1 (5.6%)
Catheter site pruritus	0	1 (6.2%)	1 (5.6%)
Chest pain	0	1 (6.2%)	1 (5.6%)
Epiphyses delayed fusion	0	1 (6.2%)	1 (5.6%)
Epistaxis	0	1 (6.2%)	1 (5.6%)
Gastroenteritis	0	1 (6.2%)	1 (5.6%)
Joint effusion	0	1 (6.2%)	1 (5.6%)
Nasal congestion	0	1 (6.3%)	1 (5.6%)
Nausea	0	1 (6.3%)	1 (5.6%)
Edema peripheral	0	1 (6.3%)	1 (5.6%)
Pyrexia	0	1 (6.3%)	1 (5.6%)
Rotavirus infection	0	1 (6.3%)	1 (5.6%)
Vertigo	0	1 (6.3%)	1 (5.6%)
Vessel puncture site erythema	0	1 (6.3%)	1 (5.6%)

Source: Reviewer-generated; adae.xpt; Software: JMP 16
[1] Treatment-emergent adverse events defined as all AEs that start on or after the first dosing day and time/start time.
[2] Treatment duration is 4 to 7 days.
Coded as MedDRA preferred terms
Abbreviation(s): N, total number of subjects in the safety population; n, number of subjects with TEAEs; TEAE, treatment-emergent adverse event

7.6.1.6. Laboratory Findings, Study B1791089

Safety labs were obtained at screening and the day after the last dose in this study. There were no clinically meaningful abnormalities in laboratory findings. There was no laboratory evidence for the known AEs such as hyponatremia, hypokalemia, or hypomagnesemia in this short-term (4 to 7 days) study of IV pantoprazole. Some noteworthy laboratory findings are summarized. Follow-up data were not available.

- Subject (b) (6) (3 y/o male) had an elevated serum potassium level (7.2 mEq/L) on study day 5, relative to baseline (4.9 mEq/L) and reference range (3.5 to 5.1 mEq/L).
- Subject (b) (6) (4 y/o) experienced a postdose reduction in serum hemoglobin from 12.8 g/dL on day-2 to 11.1 g/dL on day 7 (1.7 g/dL decrease from baseline). Subject had reported mild TEAEs of aphthous ulcer and bacterial rhinitis.
- Subject (b) (6) (8 y/o male) had a decrease in lymphocyte count from baseline to <0.5 ($10^3/mm^3$) [screening: 1.88; day 4: 0.21]. The subject had a mild TEAE of gastroenteritis and an SAE of rotavirus infection on day 4, leading to hospitalization. The lymphopenia event could potentially be related to these events.

7.6.1.7. Assessment of Drug-Induced Liver Injury, Study B1791089

No subjects demonstrated a signal for drug-induced liver injury or cholestasis in this study.

7.6.1.8. Vital-Sign Analyses, Study B1791089

Clinically meaningful changes in vital signs (blood pressure, pulse rate, temperature) were not identified in the study. While subjects on occasion exhibited either an increase or decrease in vital signs, including both the systolic and diastolic blood pressures, there were no definitive trends within or among the study subjects. In addition, the median and interquartile range for systolic and diastolic blood pressures during the 7 days of the study remained relatively within the normal range.

7.6.1.9. Subgroup Analyses, Study B1791089

Given the single-arm, uncontrolled study design and the small number of subjects reporting AEs, no meaningful subgroup analyses could be performed.

7.6.2. Safety Summary From Legacy Wyeth Studies in Pediatric Patients

The Applicant included data from pediatric studies using either oral Protonix granules or tablets or IV dosing that were previously submitted and reviewed under NDA 22020/NDA 20987. Studies were not reviewed in detail again.

Overall, the safety of oral Protonix was comparable in adults and pediatric subjects (with and without EE) including in infants with symptomatic GERD (not a labeled indication). The IV Protonix labeling includes only one additional AE, thrombophlebitis, as unique to the IV route.

Relevant Excerpts From the Approved Labeling for Oral Protonix

- Safety trials involved pediatric subjects with EE; however, as EE is uncommon in the pediatric population, 249 pediatric subjects with endoscopically proven or symptomatic GERD were also evaluated. All adult adverse reactions to Protonix are considered relevant to pediatric patients. In patients ages 1 year through 16 years, the most commonly reported (>4%) adverse reactions include URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain.
- Additionally, the label lists the following adverse reactions with a frequency of ≤4% in the oral Protonix trials in pediatric subjects: allergic reaction, arthralgia, constipation, dizziness, elevated creatine kinase, elevated liver enzymes, elevated triglycerides, facial edema, flatulence, myalgia, nausea, urticaria, and vertigo.
- In reference to a population of 129 infants 1 to 11 months of age with symptomatic GERD, the oral Protonix label further notes that the "adverse reactions that were reported more commonly (difference of ≥4%) in the treated population compared to the placebo population were elevated creatine kinase, otitis media, rhinitis, and laryngitis."

Labeling for IV pantoprazole includes the following statement: "The number of patients treated in comparative studies with PROTONIX I.V. is limited; however, the adverse reactions seen were similar to those seen in the oral studies. Thrombophlebitis was the only new adverse reaction identified with PROTONIX IV."

Legacy studies 3001K1-117-US and 3001K1-110-US evaluated the PK, PD, and safety of single IV doses of pantoprazole 0.8 mg/kg or 1.6 mg/kg infused over 15 minutes in hospitalized pediatric subjects 1 to <2 years of age (N=4), and 2 to 16 years (N=19), respectively. Treatment was generally well tolerated and no TEAEs were noted during the IV treatment period. Adverse events, some serious, were noted in the follow-up period and were deemed unrelated to the study drug and confounded by complicated medical history of the pediatric subjects. A brief overview of the safety information from the legacy IV studies is included in Section 17 of this review.

7.6.3. Safety Findings From Study B1791096

Study B1791096 was a retrospective, single-arm cohort study using patient data from EHR. The study assessed the safety of IV pantoprazole in 1,879 infants 1 to 11 months of age (Cohort 1) and 981 subjects 1 to <2 years of age (Cohort 2). Within Cohort 1, 851 (45.3%) subjects had a diagnosis of GERD without EE, Within Cohort 2, 462 (47.1%) had a diagnosis of GERD without EE.[15] The study evaluated 25 prespecified SOIs listed below:

> Agranulocytosis, thrombocytopenia, leukopenia, pancytopenia, hypersensitivity (including anaphylactic reactions and anaphylactic shock), hyperlipidemia, hypertriglyceridemia, hyponatremia, hypomagnesaemia, hypocalcemia, hypokalemia,

[15] In Study B1791096, 54.7% of subjects in Cohort 1 and 52.9% of subjects in Cohort 2 had neither a diagnosis of GERD nor EE, and therefore are not discussed further in this review. See Section 15.2.

diarrhea, vomiting, abdominal distension, hepatobiliary injury, urticaria, angioedema, SJS, TEN, erythema multiforme, DRESS, tubulointerstitial nephritis, photosensitivity, peripheral edema and injection site thrombophlebitis.

Refer to Section 15 for study design, limitations, as well as relevant tables. The clinical relevance of the observed incidence rates for the 25 prespecified SOIs and any differential outcomes across age cohorts, disease subgroups, or duration of use remains uncertain due to the study limitations including lack of a comparator group, inadequate dosing information, and dosing frequency (e.g., a gap of <7 days between treatment dates was allowed within an episode). The study was not designed to assess the causality of the SOIs, and an impact of the subjects' underlying disease, including GERD, comorbidities, and concomitant medications on the adverse outcomes cannot be ruled out.

In the DEPI review of the observational cohort study B1791096 dated February15, 2024, DEPI noted that findings are consistent "with the known safety profile of pantoprazole" to the extent that the product information for Protonix IV currently labels (directly or indirectly) each of the 25 B1791096 SOIs as either a Section 5 or Section 6 adverse reaction. DEPI notes, however, that B1791096 provided limited capacity to produce evidence contrary to the "known safety profile of pantoprazole." Reviewers also note that B1791096 used a weak method for detecting AEs not anticipated by the product information for Protonix IV.

7.7. Key Safety Review Issues

7.7.1. Safety in Infants 3 to 11 Months of Age

Issue

Lack of clinical trial safety data for Protonix IV in infants 3 to 11 months of age.

Background

(b) (4) Infants 1 to 11 months of age were not enrolled in the PK and safety Study B1791089.

The Applicant used a PK modeling and simulation approach to estimate exposures and (b) (4) dose selection in the pediatric population 1 to 11 months of age. As previously noted, the PK of IV pantoprazole in infants 1 to 11 months of age were estimated based on oral PK data, which supports extrapolation down to 3 months of age. Of note, adequate safety margins for the predicted IV pantoprazole PK in infants have been demonstrated in the juvenile animal studies. See Sections 7.1 and 13.

To support safety in infants, the Applicant submitted data from legacy studies and from the single-arm, observational cohort Study B1791096 using data from EHRs. In addition to the available safety data, the review team considered the appropriateness of leveraging safety information[2] from adults and older pediatric patients 1 to 16 years of age to support the safety of IV pantoprazole in infants 3 months to 11 months of age.

Assessment

Safety Data From Legacy Studies

Relevant safety data from legacy studies in infants 1 month to 11 months of age following oral Protonix[16] and from pediatric patients 1 to <2 years of age following IV and oral Protonix,[17] previously reviewed under NDA 22020 (S-001/S-002)[18] are summarized:

Oral Protonix Data in Infants 1 Month to 11 Months of Age

- Study 3001B3-333-WW was a PK, PD, and safety study evaluating 0.6 mg/kg (low) or 1.2 mg/kg (high) doses of pantoprazole granules for oral suspension for a duration of 5 to 10 days in infants 1 to 11 months of age with presumed GERD (81 enrolled; 67 safety). Subjects with BW of 2.5 to <7 kg were randomly assigned to receive either 2.5 mg (low) or 5 mg (high) daily doses of pantoprazole, and subjects with BW of 7 kg to ≤15 kg were randomly assigned to either 5 mg (low) or 10 mg (high) daily doses of pantoprazole.

  In this study, a total of 30 subjects had TEAEs, of which 13 (39%) subjects were in the 0.6 mg/kg dose group and 17 (50%) subjects were in the 1.2 mg/kg dose group. Treatment-emergent adverse events reported for more than 1 subject included fever (7, 10%), diarrhea (6, 9%), contact dermatitis (5, 7.5%), rhinitis (4, 6%), gastroenteritis (3, 5%), infection (3, 5%), otitis media (3, 5%), abdominal pain (2, 3%), tooth disorder (2, 3%); flatulence (2, 3%), rash (2, 3%), and vomiting (2, 3%).

  No deaths occurred in the study, and there was one study drug discontinuation due to a rotavirus infection. Serious adverse events deemed as unrelated were reported for 5 (8%) subjects, of which 3 subjects were in the 0.6 mg/kg dose group and 2 subjects were in the 1.2 mg/kg dose group, and included apnea, dehydration, gastroenteritis, stridor, and vomiting.

- Study 3001B3-329-WW was an efficacy and safety study evaluating 1.2 mg/kg (BW ≥2.5 kg to <7 kg: 5 mg; BW ≥7 kg to ≤15 kg: 10 mg) pantoprazole granules for oral suspension or matching placebo in infants 1 to 11 months of age with symptomatic GERD (154 enrolled; 129 safety). The study involved a 4-week open-label treatment run-in phase followed by a 4-week placebo-controlled treatment withdrawal phase in which subjects were stratified by weight prior to each 4-week phase.

  A total of 84 (66%) of 128 subjects had 1 or more TEAEs during the open-label phase. The most common TEAEs were URI (25; 20%), fever (13; 10%), and diarrhea (13; 10%). Other

[16] This clinical trial pre-dated the conclusions of the 2010 Gastrointestinal Drugs Advisory Committee that PPIs are unlikely to provide benefit in infants < 1 year old with symptomatic nonerosive GERD.

[17] While oral Protonix is not approved in infants with symptomatic GERD, data from a completed clinical trial of oral pantoprazole in this population did not raise any unique safety concerns in this age group.

[18] Refer to full clinical review of Protonix NDA 22020, S-001/002 (Sequence #020), finalized in DARRTs on August 10, 2009.

TEAEs that occurred in at least 5% of subjects were otitis media (12; 9%), rhinitis (11; 9%), oral moniliasis (7; 6%), vomiting (7; 6%), and cough increased (7; 6%).

During the double-blind phase, 49 (45%) of 108 randomized subjects had 1 or more TEAEs, including 25 (46%) of 54 subjects from the pantoprazole 1.2 mg/kg group and 24 (44%) of 54 subjects from the placebo group. There were no significant differences between the two treatment groups. The most common TEAE was URI, which was reported in 7 (13%) subjects in each of the treatment groups. Treatment-emergent adverse events that occurred in at least 5% of subjects in the pantoprazole 1.2 mg/kg group were fever, otitis media, vomiting, and creatine phosphokinase increased (3 (6%) subjects each). The only TEAE other than URI reported in more than 5% of subjects in the placebo group was cough increased, which was reported in 4 (7%) subjects.

Overall, the most common TEAEs in infants treated with oral pantoprazole were URIs, fever, otitis media, vomiting, and creatine phosphokinase increased.[19] Data from completed clinical trials of oral pantoprazole in infants 1 to 11 months of age did not raise any unique safety concerns in this age group.

Oral and IV Protonix Data in Pediatric Patients 1 to <2 Years of Age

- Study 3001K1-117-US was an open-label, randomized, inpatient study of the PK, safety, and tolerability of a single IV dose of pantoprazole in hospitalized pediatric patients 1 to <2 years of age (N=4). Subjects were randomized to receive either IV pantoprazole 0.8 mg/kg or 1.6 mg/kg doses, infused over 15 minutes, with a maximum dose not exceeding 40 mg.

  No TEAEs were noted during the single-dose treatment period. While SAEs were noted in two subjects during the 15-day follow-up period at each of the two IV dose levels (0.8 mg/kg and 1.6 mg/kg), these were deemed unrelated to the study drug due to the presence of these events at study entry. Refer to Section 17 for details.

- Study 3001B3-334-US was a multi-center, randomized, open-label, single and multiple dose study of the safety and PK of IV pantoprazole in pediatric patients 1 through 11 years of age with endoscopically proven GERD (66 enrolled, 41 for safety, including 17 subjects <6 years of age). Study evaluated IV pantoprazole 0.6 mg/kg (low dose; BW ≤12.5 kg: 5 mg; BW >12.5 to <25: 10 mg) and 1.2 mg/kg (high dose; BW ≤12.5 kg: 15 mg; BW >12.5 to <25: 20 mg) granules or tablets for 4 weeks duration. Study provided safety information following oral pantoprazole in the 1 to <2 years age cohort (n=2). TEAEs were noted in one of the two subjects who was randomized to the high dose and included mild, resolved events of vomiting, cough, and urinary tract infection during the treatment phase and CPK increased during the post-study phase. Overall, the study did not identify new safety signals across the pediatric age groups.

To support a reliance on safety data in infants following oral pantoprazole, the observed oral PK data from Study Wyeth 3001B3-333-WW and predicted IV systemic exposures (AUC and C_{max}) were compared in infants 3 to 11 months age. See Section 14.5. Following the proposed 0.8 mg/kg IV pantoprazole dose, the predicted maximum plasma concentration (C_{max}) and AUC values in infants 3 to 11 months of age were 4.0±0.7 µg/mL and 4.0±1.8 µg.h/mL, respectively,

[19] Full prescribing information Protonix Section 8.4 Pediatric Use
https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020987s060,022020s023lbl.pdf

compared to the C_{max} and AUC values of 1.1±0. 8 µg/mL and 3.4±2.5 µg.h/mL, respectively, observed in infants (n=12) who received 10 mg QD doses of oral pantoprazole in the legacy clinical trials, indicating a comparable AUC and a higher C_{max} following the IV route relative to the oral route.

C_{max} values bracketing those predicted in infants following an IV administration have been observed following IV dosing in pediatric subjects 1 to 17 years of age in the PK study B1791089, in the pediatric legacy IV study 3001K1-117-US, and in adults following QD 40 mg IV doses (Protonix IV, United States prescribing information). In the 1 to 2 years age group, both IV (Study 3001K1-117-US) and oral (Study 3001B3-334-US) pantoprazole were well tolerated despite higher C_{max} values following the IV route. This comparison between oral and IV pantoprazole in pediatric subjects 1 to <2 years old suggested that higher C_{max} following IV administration did not raise new safety concerns compared to oral administration. Furthermore, in the pediatric PK and safety study B1791089 and the legacy IV pantoprazole trials in adults and pediatric subjects, no acute adverse reactions associated with high C_{max} values were observed. Therefore, the safety data following oral administration in 3 to 11 months of age are considered relevant to IV administration in the same age group.

Safety Data From Study B1791096

Study B1791096 (refer to Section 15.2) included 851 infants between 1 month to 11 months of age with a diagnosis of GERD. While the study had its limitations, the findings were generally aligned with the known safety profile of pantoprazole (refer to Section 7.6.3). Additionally, while the study did not evaluate some of the known AE terms listed in the approved Protonix labels, all known adverse reactions with the use of oral or IV pantoprazole in adults as well as pediatric populations will be a part of the Protonix IV labeling.

Leveraging Available Safety Data To Support Safety in Pediatric Subjects <1 Year of Age

Although infants <1 year of age were not enrolled in Study B1791089, safety data from legacy studies in infants 1 month to 11 months of age following oral Protonix and from pediatric patients 1 to <2 years of age following IV and oral Protonix were available to inform safety in infants <1 year of age. Given the proposed duration of use up to 7 days in infants, there are no identified novel considerations in infants that would preclude applicability of safety outcomes from the use of IV and/or oral Protonix in adults or other pediatric age groups, or from related conditions, including symptomatic GERD, as many of the known adverse reactions related to PPI use relates to its long-term chronic use.

Additionally, there are well over three decades of clinical experience with the PPI drug class, and an adequate understanding of safety of PPIs in the treatment of EE in pediatric patients including infants, as well as the treatment of symptomatic nonerosive GERD in pediatric patients 1 year and older. Approved PPI products for EE include oral pantoprazole down to 5 years of age,[20] lansoprazole for patients down to 1 year of age, and oral and IV esomeprazole and oral omeprazole in patients down to 1 month of age (See Table 5).

Given that 1) differences in safety are not expected based on disease severity, including presence or absence of erosions; 2) adequate safety margins for the predicted IV pantoprazole PK in

[20] Data available down to 1 year of age, but approval limited to ≥5 years of age due to lack of age-appropriate formulation.

infants have been demonstrated in the juvenile animal studies; 3) predicted IV systemic exposures were comparable to observed oral PK data in 3 to 11 month old infants (AUC) and supported by IV pantoprazole data in pediatric subjects 1 to <2 years old (C_{max}); and 4) the safety profile is not expected to be markedly different from what is known for pantoprazole and the PPI drug class for the proposed use up to 7 days of Protonix IV in infants 3 to 11 months, overall, the safety data from use of pantoprazole in pediatric subjects with nonerosive and erosive esophagitis are relevant populations that can be leveraged to support the safety of up to 7 days of use of Protonix IV in infants 3 to 11 months of age. This approach also aligns with the principles outlined in the draft guidance for industry *E11A Pediatric Extrapolation* (April 2022).

Conclusion

Safety of IV pantoprazole for use up to 7 days in infants 3 to 11 months of age is adequately supported.

7.7.2. Safety in Pediatric Subjects With EE

Issue

Majority of subjects enrolled in Study B1791089 had a diagnosis of GERD but not necessarily a history of EE.

Background

One subject[21] in the interventional study B1791089 and none in the observational cohort study B1791096 had EE. The review team considered whether safety data of IV pantoprazole predominantly from patients with symptomatic nonerosive GERD were relevant to inform safety for the use of IV pantoprazole for up to 7 days in pediatric subjects with GERD with a history of EE. See Section 7.7.1.

Assessment

While information on subjects with EE is minimal in this pediatric supplement, it was deemed acceptable to leverage the safety data of IV pantoprazole from a pediatric population with nonerosive GERD from Study B1791089 to support a population with GERD and a history of EE for the proposed use up to 7 days until the patients can be transitioned to oral treatment. Safety of IV pantoprazole is not anticipated to be impacted by disease severity and is likely to be a function of drug dose, regimen, and duration of use. Furthermore, Protonix has been approved for oral use in adults and pediatric patients with EE associated with GERD since February 2, 2000 and November 12, 2009, respectively. Note that while the data from pediatric clinical trials supported use of oral Protonix in pediatric patients down to 1 year of age, due to the absence of a commercial dosage form in younger patients, product was approved only for pediatric patients 5 years and older. The proposed duration of use in the current submission is up to 7 days of

[21] In an IR response submitted on March 29, 2024, the Applicant noted that in Study B1791089 one subject (ID (b) (6), 15 y/o, White, male) out of the 9 subjects with a diagnosis of 'endoscopically proven GERD' (listed in Table 16.2.4.2.2. Primary Diagnoses- All Randomized Participants of the Clinical Study Report), had a confirmed erosive lesion (Los Angeles [LA] classification B) in the distal esophagus. The remaining 8 subjects did not show any evidence of an erosive lesion.

treatment with IV pantoprazole; therefore, the review team determined that safety data from IV pantoprazole in pediatric subjects with nonerosive GERD, the established safety profile of oral Protonix in adults and pediatric patients with EE associated with GERD, as well as the comparability between the observed oral PK data and predicted IV exposure as discussed in Section 7.7.1, supported the safety of up to 7 days of IV pantoprazole in pediatric patients with GERD with a history of EE.

Safety data from pediatric subjects with GERD with or without EE from the legacy Wyeth studies using oral pantoprazole (previously reviewed under NDA 22020, August 10, 2009) are summarized below:

Study 3001B3-328-NA

The study evaluated efficacy and safety of oral pantoprazole in pediatric subjects 1 to 5 years of age (N=60) with symptomatic GERD, including four subjects with EE, as assessed by endoscopy. Subjects were randomized to low (0.3 mg/kg), medium (0.6 mg/kg), or high (1.2 mg/kg) doses of oral pantoprazole spheroids. Fixed low, medium, and high doses were administered to subjects based on their age; for subjects 1 to <2 years of age, 5 mg, 10 mg, or 15 mg, respectively, and for subjects 2 to <6 years of age, 5 mg, 10 mg, or 20 mg, respectively, was administered. Subjects with EE were randomized to medium or high doses.

- Overall: Treatment-emergent adverse events were reported in 55 of 60 (92%) of the safety population. Treatment-emergent adverse events reported in three or more subjects (≥5%) included URI (38%), fever (18%), vomiting (15%), diarrhea (15%), rhinitis (15%), headache (13%), cough increased (12%), abdominal pain (8%), pharyngitis (8%), lymphadenopathy (8%), gastroenteritis (7%), ecchymosis (7%), and sinusitis (5%). Three SAEs occurred in two subjects and included abdominal pain, anorexia, and dehydration. No deaths were reported.
- Erosive esophagitis subgroup: Treatment-emergent adverse events were reported in three of four subjects with EE (1 to <2 years of age) who received doses ranging 10 mg to 20 mg QD for 8 weeks. These included fever, URI, sinusitis, pharyngitis, bronchitis, nosebleed, and runny nose. The safety of oral pantoprazole in this disease subtype was comparable to the overall safety profile that mainly included subjects with symptomatic, nonerosive GERD.

Study 3001A1-322-US

Study evaluated the efficacy and safety of oral pantoprazole in pediatric subjects 5 to 11 years of age (N=53) with symptomatic GERD, including 4 subjects with EE. Subjects were randomly assigned to 10 mg, 20 mg, or 40 mg enteric-coated pantoprazole tablets QD for 8 weeks.

- Overall: Treatment-emergent adverse events were reported by 48 (90.6%) subjects treated with pantoprazole, with 17 (89.5%) in the 10 mg group, 16 (88.9%) in the 20 mg group, and 15 (90.6%) in the 40 mg group. The most common TEAEs (≥3%) in the pantoprazole 10 mg group were headache (37%), rhinitis (26%), accidental injury and infection (21%), and nausea (16%). The most common TEAEs in the pantoprazole 20 mg group were headache (28%) and infection and rhinitis (17%). The most common TEAEs in the pantoprazole 40 mg group were headache (25%), accidental injury (31%), abdominal pain, infection, asthma, and pharyngitis (3 subjects each; 18.8%). There were no deaths, discontinuations due to safety reasons, or SAEs in this study.

- Erosive esophagitis subgroup: Treatment-emergent adverse events were reported in two subjects with EE and included rhinitis, vomiting, pain, and accidental injury. The safety of oral pantoprazole in this disease subtype was comparable to the overall safety profile that mainly included subjects with symptomatic, nonerosive GERD.

Overall, as summarized above from legacy studies, the data from pediatric subjects 1 year and older suggest a similar safety profile of pantoprazole in subjects with EE relative to those with nonerosive GERD in studies done with oral pantoprazole DR granules or tablets.

The proposed indication for Protonix IV in pediatric patients is for use up to 7 days, and safety is not expected to be markedly different to that which is generally understood for pantoprazole.

Conclusion

Safety data from symptomatic GERD can be leveraged to support safety in GERD associated with a history of EE for the proposed short-term use of Protonix IV.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Body weight is the most significant intrinsic factor that correlated with pantoprazole clearance. Age-dependent clearance after adjusting for body weight effect on pantoprazole clearance played a major role in neonates and infants <3 months old. See Section 14 for details.

8.2. Extrinsic Factors

No extrinsic factors were evaluated and proposed in this supplement NDA submission.

8.3. Plans for Pediatric Drug Development

NDA 20988/S-070 fulfills the following pending PREA PMRs for Protonix IV:

- 255-6: Deferred pediatric study under PREA for the short-term treatment (7 to 10 days) of GERD, as an alternative to oral therapy in patients who are unable to take Protonix (pantoprazole sodium) DR Tablets in patients 2 to 16 years of age *[Issued March 22, 2001]*
- 145-1: Deferred pediatric study under PREA for the treatment of GERD in pediatric patients ages 0 to 16 *[Issued on December 6, 2004]*

In the context of PMR 145-1, although the original PMR 145-1 language included down to birth, that does not align with the currently recommended approach to these studies and accordingly a partial waiver will be granted for studies in neonates (<1 month) based on 21 CFR 314.55I(3)(ii) as EE is rare in this age group, making studies impossible or highly impracticable.

With respect to infants 1 to 11 months of age also included in PREA PMR 145-1, as previously explained, the Population PK model could not reliably predict exposures in infants <3 months of age, thus precluding approval in the 1 to <3 months age group. See Section 6.

The review team and PeRC considered the challenges with enrolling pediatric patients 1 month to <3 months of age in clinical trials and the efforts the Applicant has put forth in addressing this age group. In light of these considerations, the Applicant is unlikely to be able to obtain additional, interpretable data in patients 1 month to <3 months of age. Further, conducting studies at this time in only 1 month to <3 months of age patients with GERD with a history of EE to obtain information for IV pantoprazole for up 7 days of use would be infeasible. The PeRC agreed that the Applicant's submission fulfills PMR 145-1, which encompasses infant age range <3 months, and that no additional assessments would be required to address infants 1 to 3 months of age.

Overall, the approval of this supplemental application for Protonix IV fulfills the previously deferred PREA PMRs 255-6 and 145-1. No additional pediatric development or new PMRs are required.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

No reproductive and developmental toxicity study reports were submitted in this supplement. The reproductive and developmental toxicity studies of pantoprazole were performed in rats and rabbits. The studies were reviewed previously. No labeling changes are recommended for the nonclinical sections of the label.

9. Product Quality

Approval

The Office of Pharmaceutical Quality review team has assessed NDA 20988/S-070 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. Therefore, the Office of Pharmaceutical Quality recommends approval of this sNDA from a quality perspective.

There are no product quality (Module 3) updates associated with this submission; hence, no quality overall summary or reports are included. There are no changes to the sections of the full prescribing information relevant to chemistry, manufacturing, and controls (sections 2, 3, 11, and 16).

The request for Categorical Exclusion according to 21 CFR Part 25.15 (a), (d) to prepare environmental assessment is found acceptable based on the calculation showing the estimated concentration of the drug substance at the point of entry into the aquatic environment is well below the 1 parts per billion limit, and the Applicant's claim that, to the best of their knowledge, no extraordinary circumstances exist.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Study B1791089 was conducted in accordance with International Council for Harmonisation good clinical practices and other applicable guidelines, laws, and regulations, including privacy laws. Subjects or their legally authorized representative signed a statement of informed consent that met the requirements including for 21 CFR 50, International Council for Harmonisation guidelines, and the Health Insurance Portability and Accountability Act.

Financial disclosure reports (Form FDA 3454) were obtained for all 33 clinical investigators in the covered study B1791089. All investigators disclosed as having no financial interest in the product. There were no investigators who were full-time or part-time employees of the Applicant.

11. Advisory Committee Summary

An advisory committee meeting was not deemed necessary for the review of this application.

III. Additional Analyses and Information

12. Summary of Regulatory History

On March 22, 2001, the Applicant received original marketing approval for Protonix (pantoprazole sodium) IV for the short-term (7 to 10 days) treatment of gastroesophageal reflux disease (GERD) as an alternative to oral therapy in patients who are unable to take Protonix (pantoprazole sodium) delayed-release tablets. Following the original approval, the Applicant submitted supplement 03 and received approval to for the use of Protonix IV for the treatment of pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome or other neoplastic conditions on October 19, 2001.

This NDA is subject to multiple outstanding postmarketing requirements (PMRs) under the Pediatric Research Equity Act (PREA). At the time of the original approval, PMR 255-6 ("Deferred pediatric study under PREA for the treatment of for short-term treatment [7 to 10 days] of gastroesophageal reflux disease [GERD], as an alternative to oral therapy in patients who are unable to take Protonix [pantoprazole sodium] Delayed-Release Tablets in patients 2 to 16 years of age") was issued. Following the approval of supplement 27, PMR 145-1 ("Deferred pediatric study under PREA for the treatment of GERD in pediatric patients ages 0 to 16") was issued.

FDA issued a letter on August 9, 2011, concluding the PMRs were not met in response to the submission of final study reports and provided descriptions of what studies would be needed to fulfill the PREA requirements. On May 30, 2013, FDA issued a letter denying the Applicant's deferral extension request. A Notification of Non-Compliance with PREA letter was subsequently issued on June 14, 2013.

A type C meeting request was submitted on August 9, 2013, to gain agreement with FDA for proposed protocol B2851006 to satisfy PREA requirements as described in the August 9, 2011, FDA letter. Advice was provided by FDA in written responses sent on November 8, 2013. The Agency ultimately provided a letter on October 9, 2015, agreeing to a November 14, 2014, submission of protocol B1791089 (formerly B2851006) as the final to meet requirements for both PREA PMRs

On April 3, 2013, FDA provided written responses to a type C meeting to discuss proposed revisions to protocol B1791089 to adequately address the PMRs and discuss the <1 year of age cohort of PMR 145-1. FDA agreed with the Applicant's proposal to request a partial wavier of PMR 145-1 for subjects aged 0 to 1 month. Furthermore, FDA recommended the Applicant to submit a request for release of PMRs 255-6 and 145-1 followed by a request for a new PMR, stating a final decision will be made after discussion with the Pediatric Review Committee. On February 22, 2019, the Applicant submitted protocol amendments and the requests as described in the written responses. An Advice Letter was issued on February 5, 2021, stating the release and reissuance of the PMRs were not appropriate after discussion with the Pediatric Review Committee and that the Applicant should complete the planned clinical trials. FDA stated the partial waiver of subjects <1 month of age should be requested in a future efficacy supplement and acknowledged the Applicant's approach to utilize a pharmacokinetic (PK) modeling/simulation in lieu of an interventional clinical trial for infants aged 1 to 11 months.

A type B meeting was requested on October 11, 2022, to discuss newly available PK and safety data from the ongoing pediatric study B1791089, data from the completed study B1791096, and data from legacy Wyeth studies to provide sufficient information to both PREA PMRs. The videoconference was cancelled by the Applicant after receipt of FDA preliminary comments on December 12, 2022. Lastly, preliminary comments were issued on May 9, 2023, to a pre-sNDA meeting request. The videoconference was cancelled by the Applicant after receipt of the preliminary comments.

The purpose of this supplement is to fulfill outstanding PREA requirements 255-6 and 145-1 and support the indication for the treatment (up to 7 days) of pediatric patients with GERD and a history of EE. This submission provides proposed labeling changes and the data derived from the conducted pediatric studies.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

No new nonclinical study reports have been submitted in this supplement. Previously submitted toxicity studies of pantoprazole in neonatal/juvenile rats and dogs were reviewed under the IND 35441, IND 52132, IND 68011, and NDA 22020/S001, NDA 22020/S002, NDA 20987/S036 and NDA 20987/S037. The finding of the studies are similar to the findings observed in adult animal toxicology studies, and do not raise any significant safety concerns.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

No new nonclinical study reports have been submitted in this supplement. The reports of the previously submitted nonclinical studies with pantoprazole sodium were reviewed as part of the initial and supplemental marketing applications for use of pantoprazole sodium in adults and pediatric patients.

14. Clinical Pharmacology

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

Study B1791089

Study B1791089 was a non-randomized, open-label, multicenter study to characterize the pharmacokinetics of single and multiple IV doses of pantoprazole in hospitalized pediatric subjects 1 to 16 years of age. See study details in Section 15.1.

In pediatric subjects 1 to <2 years of age, PK samples were collected on study Day 1 at 0. 25 (end of the 15-minute infusion), 0.5, 1, 2, 4, 8, and 12 hours after the start of the infusion; on Day 7 at pre-dose and 0.25 (end of the 15-minute infusion), 0.5, 1, 2, 4, 8, and 12 hours after the start of the infusion. In pediatric subjects 2 to 16 years of age, PK samples were collected on study Day 1 at 0.25 (end of the 15-minute infusion), 0.5, 0.75, 1, 1.5, 2, 4, 8, and 12 hours after the start of the infusion; on Day 7 at pre-dose and at 0.25 (end of the 15-minute infusion), 0.5, 0.75, 1, 1.5, 2, 4, 8, and 12 hours after the start of the infusion. PK parameters were estimated based on population PK analysis (see Section 14.5 below). The summary statistics of steady state AUC and C_{max} are presented in Table 15.

Table 15. Summary of Observed Steady State PK Parameters in Study B1791089 and in Adults

Age	Dose	AUC (µg.h/mL)	C_{max} (µg/mL)
1 to 2 years old		6.5±4.3	5.7±3.0
2 years old and older		7.7±4.2	4.9±2.6
Adults	40 mg	6.02±4.18	6.26±3.01

Source: Table 14.4.5.1 in Clinical Study Report B1791089

14.3. Bioanalytical Method Validation and Performance

The PK of pantoprazole following IV or oral administration were characterized in pediatric subjects ≤16 years old in the following studies (see Table 16 below).

Table 16. PK Data Included in the PopPK Analysis

Study	N	Population	Doses
B1791089 Multiple IV dose PK study	18	Hospitalized pediatric subjects 1 to 16 years of age who are candidates for acid suppression therapy	10 mg (age =1 - <2 years, n=2) 20 mg (age =3 – 9 years, n=9) 40 mg (age =9 – 16 years, n=7)
Wyeth 3001K1-110-US Single IV dose PK study	18	Hospitalized pediatric patients aged 2 to 16 years, inclusive, who could benefit from acid suppression therapy	0.8 mg/kg (n=9) 1.6 mg/kg (n=9)
Wyeth 3001K1-117-US Single IV dose PK study	4	Hospitalized male and female patients at least 1 year but less than 2 years of age who, in the judgment of the investigator, would benefit from acid suppression therapy.	0.8 mg/kg (n=2) 1.6 mg/kg (n=2)
Wyeth 3001A3-337-US Single/Multiple oral dose PK study	21	Adolescents aged 12 through 16 years with GERD	20 mg, 40 mg

Study	N	Population	Doses
Wyeth 3001B3-334-US Single/Multiple oral dose PK study	40	Children aged 1 through 11 years with endoscopically proven GERD	5 mg, 10 mg, 15 mg, 20 mg, 40 mg
Wyeth 3001B3-333-WW Single/Multiple oral dose PK study	64	Infants aged 1 through 11 months with presumed GERD	0.6 mg/kg, 1.2 mg/kg
Wyeth 3001B3-331-WW Oral dose PK study	55	In neonates and preterm infants with a clinical diagnosis of GERD	1.25 mg, 2.50 mg

Source: Adapted from Table 7 in Report PMAR-EQDD-B179a-sNDA-1153
Abbreviation(s): GERD, gastroesophageal reflux disease; IV, intravenous; PK, pharmacokinetic; PopPK, population pharmacokinetic

Studies Wyeth 3001K1-110-US, Wyeth 3001K1-117-US, Wyeth 3001A3-337-US, Wyeth 3001B3-334-US, Wyeth 3001A3-333-WW, and Wyeth 3001A3-331-WW were originally submitted under NDA 022020 sequence number 0020 on November 21, 2008, including the clinical study reports, method validation reports, and bioanalytical reports. See details in Table 17 below.

Table 17. List of Bioanalytical Methods

Study	Method Validation Report	Bioanalytical Report	NDA and Sequence Number
B1791089	B1799001	8321-091	NDA020988\0140
Wyeth 3001K1-110-US	GTR-30693 (V1265P1, HPLC/UV)	RPT-45858	NDA022020\0020
Wyeth 3001K1-117-US	RPT-54260 (V2191P1, HPLC/MS)	RPT-57362	
Wyeth 3001A3-337-US	RPT-54260 (V2191P1W)	RPT-66312	
Wyeth 3001B3-334-US		RPT-62839	
Wyeth 3001B3-333-WW		RPT-62840	
Wyeth 3001B3-331-WW		RPT-62842	

Source: reviewer generated
Abbreviation(s): HPLC, high-performance liquid chromatography; MS, mass spectrometry; NDA, new drug application; UV, ultraviolet

Bioanalytical method validation for GTR-30693 and RPT-54260 were previously reviewed by Dr. Insook Kim under NDA 022020 SE5 DARRTS on August 13, 2009, for clinical studies 109, 110, and 114.

Method B1799001, the PK bioanalytical method for Study B1791089, was submitted under NDA 020988 SDN0140 on October 31, 2023, to support efficacy supplement 070. A summary of the bioanalytical method validation is listed in Table 18 below.

Table 18. Bioanalytical Method B1799001 Validation Summary

Report Title	The Validation of a HPLC-MS/MS Method for the Determination of Pantoprazole in Lithium Heparin Human Plasma	
Pfizer Validation Plan Number	B1799001	
Pfizer Sponsor Location	New York	
Pfizer Principal Contact	Penelope Crownover	
Bioanalytical Laboratory	(b) (4)	
Bioanalytical Laboratory Project Reference	8301-415	
Bioanalytical Laboratory Method Number	PANHPP	
Principal Bioanalytical Investigator	(b) (4)	
Method Description		
Reference Standard(s)	Pantoprazole (a.k.a. PF-05208751), Lot 1-SWM-19-1	
Internal Standard	Pantoprazole-d7, Lot 8-CGJ-82-4	
Matrix	Human Plasma	
Anticoagulant	Lithium Heparin	
Source of Control Matrix	(b) (4)	
Sample Storage Temperature	-20°C	
Extraction Method	Liquid/Liquid Extraction	
Detection Method	HPLC-MS/MS	
Sample Aliquot Volume	20.0 µL	
Regression, Weighting	Linear, 1/concentration squared	
Quantification	Peak Area Ratios	
Calibration Range	5.00 to 5000 ng/mL	
ULOQ	5000 ng/mL	
LLOQ	5.00 ng/mL	
Validation (VQC) Sample Concentrations	5.00, 15.0, 250, 4000 and 15000 (dilution VQC) ng/mL	
Assay Performance		
Intra-Assay Validation (VQC) Sample Statistics	Precision (%CV) ≤6.9%	Accuracy (%RE) -8.6% to 3.3%
Inter-Assay Validation (VQC) Sample Statistics	Precision (%CV) ≤5.9%	Accuracy (%RE) -4.6% to 1.6%
Dilution Factors	10-fold	
Mean Analyte Recovery	39.1%	
Mean Internal Standard Recovery	31.7%	

Source: Method Validation Report B1799001 Page 5
Abbreviation(s): CV, coefficient of variation; HPLC, high-performance liquid chromatography; LLOQ, lower limit of quantification; MS, mass spectrometry; RE, relative error; ULOQ, upper limit of quantification; VQC, validation quality control

Bioanalytical Method B1799001 met the requirements for bioanalytical assay and is acceptable.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

The Applicant conducted a population pharmacokinetics (PopPK) analysis to characterize pantoprazole PK in children 1 month to 16 years old. The pantoprazole PopPK analysis consisted of 220 subjects (40 subjects receiving IV pantoprazole dosing and 180 subjects receiving oral dosing) contributing a total of 1085 plasma pantoprazole concentrations (323 following IV dosing; 762 following oral dosing) from seven different clinical studies with pediatric subjects from birth to 16 years of age. Studies that were included in the PopPK analysis are listed in Table 16 above.

The PK of pantoprazole were characterized by a two-compartment model with first order elimination and first order absorption in children. Body weight (BW) effect by allometric scaling on volume(s) of distribution, clearance (CL) and Q were included in PopPK analysis using a power model with fixed exponents of 0.75 for CL and Q and 1 for Vc and Vp. The reference BW was 10 kg. CYP2C19 poor metabolizer status effect on CL was also included. The final PK parameter estimates are listed in Table 19 below.

Table 19. Final PK Parameter Estimates

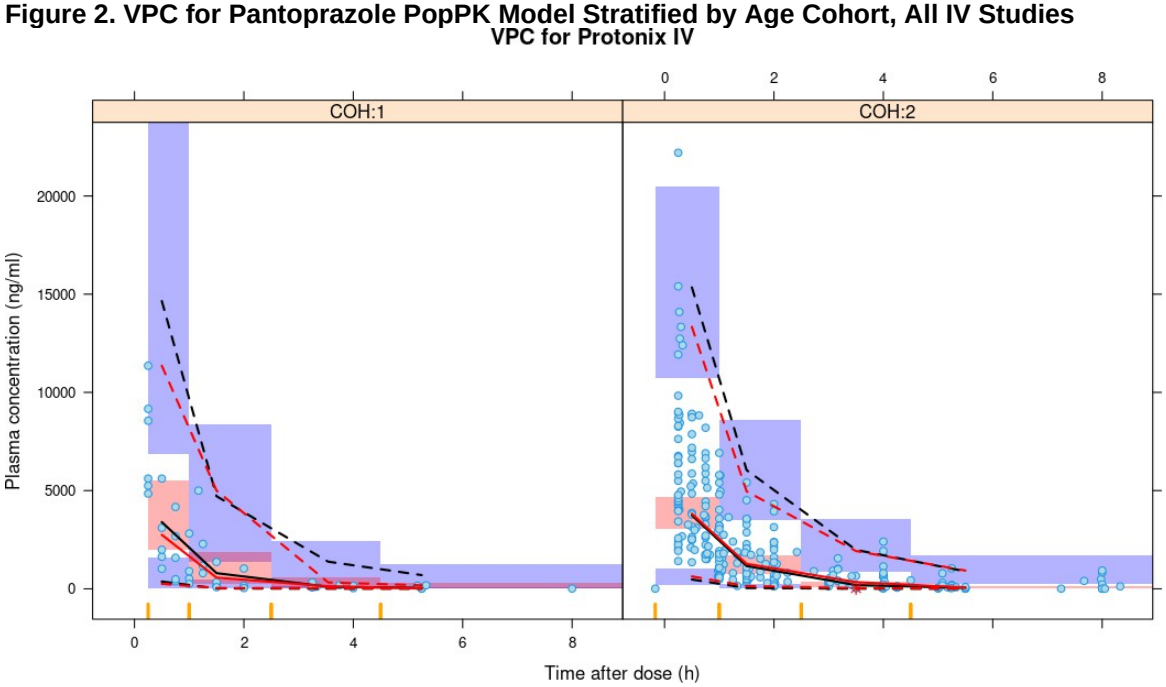
Parameter	Estimate	RSE [%]	CV [%]
CL [L/h] (θ_1)	2.04	7.71	
×(WT/10)$^{\theta_{10}}$	0.75 (fixed)	-	
$Hill_{CL}$ (θ_{12})	1.52	14.0	
AG50 (θ_{13})	0.142	25.7	
AG50preterm (θ_{14})	1.38 (fixed)	-	
×SEX_{CL} (θ_{15})	1 (fixed)	-	
×$CPH1_{CL}$ (θ_{16})	0.0758	44.7	
×$Race_{CL}$ (θ_{17})	1.29	10.6	
Vc [L] (θ_2)	1.52	8.41	
×(WT/10)$^{\theta_{11}}$	1 (fixed)	-	
Q [L/h] (θ_3)	0.190	33.6	
×(WT/10)$^{\theta_{10}}$	0.75 (fixed)	-	
Vp [L] (θ_4)	0.660	25.1	
×(WT/10)$^{\theta_{11}}$	1 (fixed)	-	
KA tablet[h^{-1}] (θ_5)	1.43	12.1	
Tlag [h] (θ_6)	0.436	4.33	
F1 tablet (θ_7)	1 (fixed)	-	
F1 spheroid (θ_8)	0.318	16.5	
KA spheroid [h^{-1}] (θ_9)	0.598	13.9	
IIV			
CL($\Omega_{1.1}$)	0.382	15.4	61.8
COV_{CLV}($\Omega_{2.1}$)	0.0985	71.8	r =0.39
Vc($\Omega_{2.2}$)	0.165	25.2	40.7
KA($\Omega_{3.3}$)	0.610	28.4	78.1
$F1_{IOV}$ ($\Omega_{4.4}$)	0.328	24.9	57.3

Parameter	Estimate	RSE [%]	CV [%]
Residual Errors			
Prop IV (σ_1)	0.145	22.3	38.1
Prop Tab(σ_2)	0.343	17.9	58.6
Add*(ng/mL) (σ_3)	32.1	71.5	SD =5.66
Prop Sph (σ_4)	0.323	9.26	56.8

Source: Table 8 in Report PMAR-EQDD-B179a-sNDA-1153
Abbreviation(s): CL, clearance; COV, covariance; CV, coefficient of variation; IIV, interindividual variability; IV, intravenous; KA, absorption rate constant; PK, pharmacokinetic; Q, intercompartmental clearance; RSE, relative standard error; SD, standard deviation; Sph, spheroid; Tab, tablet; Tlag, lag time; V_c, volume of central compartment; Vp, volume of peripheral compartment; WT, body weight

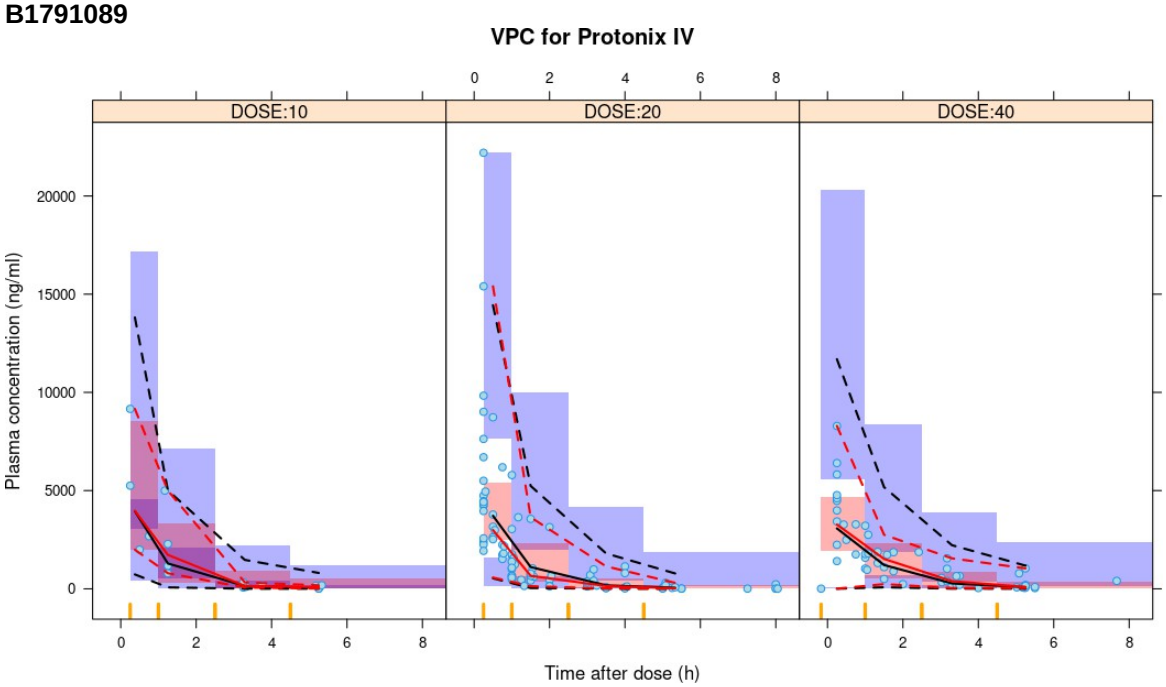
Visual predictive check plots by age cohort and dose are depicted in Figures Figure 2 and Figure 3 below.

Figure 2. VPC for Pantoprazole PopPK Model Stratified by Age Cohort, All IV Studies



Source: Figure 3 in Report PMAR-EQDD-B179a-sNDA-1153
COH 1 refers to age group 1 - <2 years of age and COH 2 refers to age group 2 – 16 years of age
Abbreviation(s): COH, cohort; h, hour; IV, intravenous; PopPK, population pharmacokinetic; VPC, visual predictive check

Figure 3. VPC for Pantoprazole PopPK Model Stratified by Pantoprazole Dose Given, Study B1791089



Source: Figure 4 Report PMAR-EQDD-B179a-sNDA-1153
DOSE: 10 corresponds to subjects <15 kg receiving 10 mg daily dose, DOSE: 20 corresponds to subjects 15 to <40 kg receiving 20 mg daily dose and DOSE: 40 corresponds to subjects ≥40 kg receiving 40 mg daily dose
Abbreviation(s): h, hour; IV, intravenous; PopPK, population pharmacokinetic; VPC, visual predictive check

The Applicant conducted simulation-based assessment on the systemic exposure (AUC and C_{max}) of pantoprazole in children 1 year and older and 1 month to <1 year old following the proposed IV dosing regimens. The virtual population was resampled with replacement from the Centers for Disease Control and Prevention growth chart (weight-for-age).

Summary statistics of BW and age in children 1 year and older resampled from the Centers for Disease Control and Prevention growth chart (weight-for-age) are listed in Table 20.

Table 20. Demographics by Body Weight Group

BW Group	n	BW (min)	BW (Q25)	BW (Q50)	BW (Q75)	BW (max)
<15 kg	1385	7.5	10.7	11.9	13.1	15.0
>15 – 40 kg	1630	15.0	18.5	23.4	30.5	40.0
>40 kg	985	40.0	45.3	51.3	59.4	105.7
BW Group	**n**	**AGE (min)**	**AGE (Q25)**	**AGE (Q50)**	**AGE (Q75)**	**AGE (max)**
<15 kg	1387	1.0	1.4	1.7	2.2	5.4
>15 – 40 kg	1616	1.4	5.1	7.3	9.8	15.6
>40 kg	997	5.7	12.8	14.0	15.1	16.0

Source: Table A9.4 in Report PMAR-EQDD-B179a-sNDA-1153
Abbreviation(s): BW, baseline body weight (kg); max, maximum value; min, minimum value; n, number of subjects; Q25, 25th percentile; Q50, 50th percentile; Q75, 75th percentile

Simulations based on the final PopPK model were performed for a 15-minute pantoprazole IV infusion of 10 mg, 20 mg, or 40 mg depending on the BW. The simulated AUC and C_{max} are

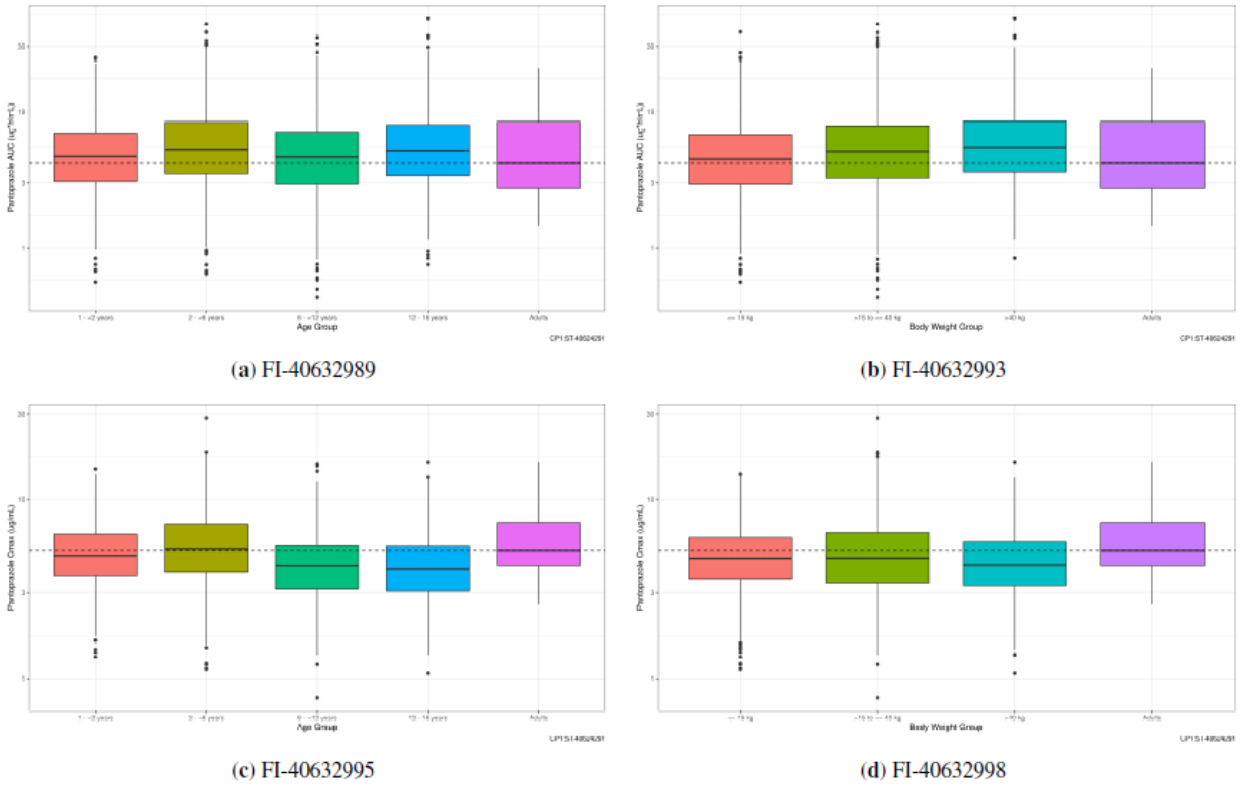
listed in Table 21 below. Both AUC and C_{max} in each age and BW cohort were comparable to the observed data in adults.

Table 21. Simulated AUC and C_{max} in Children 1 Year and Older Following the (b) (4) Dosing Regimens

Age	Body Weight	Dose	AUC (µg.h/mL)	C_{max} (µg/mL)
1 to 2 years old	<15 kg	10 mg	5.7±4.0	5.6±2.6
	15 to <40 kg	20 mg	8.7±5.7	7.7±2.8
2 years old and older	8 to <15 kg	10 mg	4.9±3.6	4.6±2.0
	15 to <40 kg	20 mg	6.2±4.6	5.2±2.7
	40 kg and above	40 mg	6.7±4.6	4.7±2.0
Adults		40 mg	6.02±4.18	6.26±3.01

Source: reproduced based on protonix-iv-1-16y-run16.tab and protonix-iv-1y-2y-run15.tab
Abbreviation(s): AUC, area under the concentration-time curve; C_{max}, peak serum drug concentration

Figure 4. Exposure Box Plots on Log-Scale for IV Doses of 10 mg (BW ≤15 kg) 20 mg (BW 15 kg to ≤40 kg) and 40 mg (>40 kg)



(a) FI-40632989 (b) FI-40632993

(c) FI-40632995 (d) FI-40632998

Source: Figure 12 in Report PMAR-EQDD-B179a-sNDA-1153
Repository artifact IDs are shown in subfigure labels.
(a) Pantoprazole AUC box plots per age group (1000 profiles per pediatric age group)
(b) Pantoprazole AUC box plots per BW group
(c) Pantoprazole C_{max} box plots per age group (1000 profiles per pediatric age group)
(d) Pantoprazole C_{max} box plots per BW group
Adult exposure values (n=55) correspond to individual parameters obtained from NCA following 40 mg IV dose
Abbreviation(s): BW, baseline body weight (kg); IV, intravenous

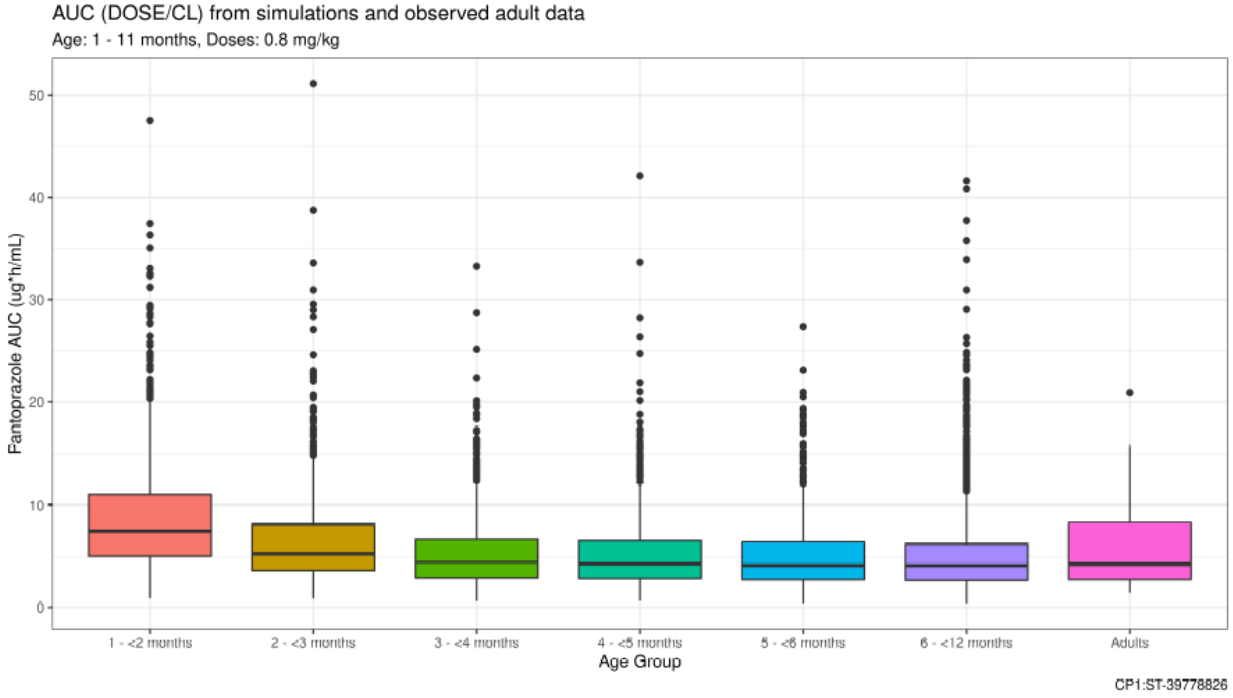
Summary statistics of simulated BW and PK parameters following the proposed dosing regimen in infants <1 year old are listed in Table 22. The distribution of AUC and C_{max} are depicted in Figure 5.

Table 22. Simulated Body Weight and PK Parameters in Infants <1 Year Old

Age Group	n	Body Weight (kg)	C_{max} (µg/mL)	C_{max} Ratio	AUC (µg·h/mL)	AUC Ratio
1 - <2 m	1000	4.7 (2.9-6.7)	4.7 (2.21-9.81)	0.91	7.46 (2.47-24.09)	1.78
2 - <3 m	1000	5.5 (3.1-7.9)	4.58 (2.02-10.34)	0.89	5.27 (1.59-18.44)	1.25
3 - <4 m	1000	6.1 (3.9-8.8)	4.41 (2.04-9.37)	0.85	4.45 (1.35-14.37)	1.06
4 - <5 m	1000	6.7 (4.4-10.4)	4.36 (2.15-9.16)	0.84	4.24 (1.37-14.59)	1.01
5 - <6 m	1000	7.3 (5-10.7)	4.37 (2.1-8.96)	0.85	4.1 (1.25-14.53)	0.98
6 - <7 m	1000	7.8 (5.3-11.5)	4.35 (2.03-9.4)	0.84	4.19 (1.18-14.21)	1
7 - <8 m	1000	8.3 (5.7-12.7)	4.36 (2.1-9.31)	0.84	4.09 (1.27-13.68)	0.97
8 - <9 m	1000	8.7 (5.7-12.8)	4.26 (1.94-8.59)	0.83	4.01 (1.21-12.58)	0.96
9 - <10 m	1000	9 (6.2-12.8)	4.22 (1.91-8.69)	0.82	4.03 (1.25-12.8)	0.96
10 - <11 m	1000	9.5 (6.7-14.1)	4.26 (2.01-8.86)	0.83	4.19 (1.31-13.43)	1
11 - <12 m	1000	9.8 (6.5-15.8)	4.26 (2.09-9.01)	0.83	4.03 (1.24-13.16)	0.96
Adults	55	NA	5.16 (2.94-12.51)	1	4.2 (2.05-15.02)	1

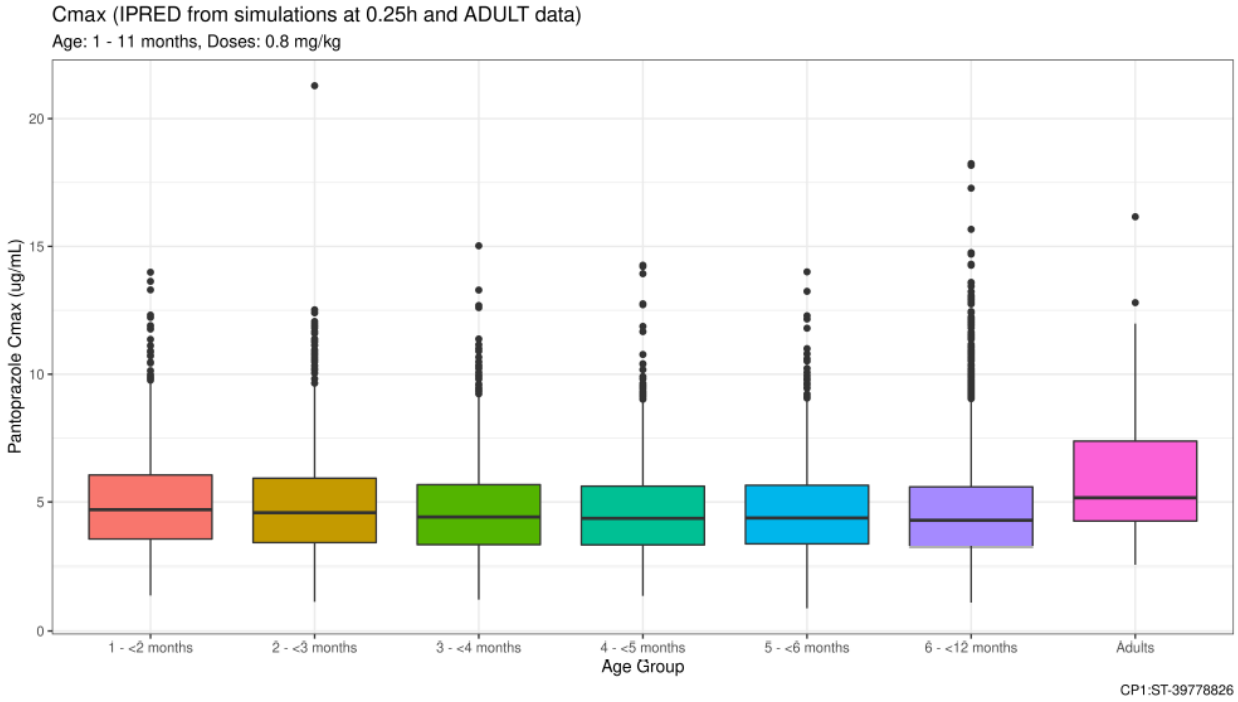
Source: Table 3 in Report PMAR-EQDD-B179a-sNDA-1294.
n = number of simulated profiles (Groups <12 m) or number of subjects (Adults). Body weight corresponds to median (range) and C_{max} and AUC correspond to median (2.5th and 97.5th percentiles), C_{max} ratio and AUC ratio correspond to median of individual pediatric to adult ratio (obtained by dividing the exposure parameter for each simulated pediatric profile by the adult median exposure parameter) for each age group.
Abbreviation(s): AUC, area under the concentration-time curve; C_{max}, maximum plasma drug concentration; m, month(s); n, number of subjects in age group; NA, not available; PK, pharmacokinetic

Figure 5. Pantoprazole AUC and C_{max} Box and Whisker Plot for an IV Dose of 0.8 mg/kg (10 mg for Body Weight ≥12.5 kg) Compared to Observed AUC and C_{max} in Adults (40 mg IV Dose)



Continued

Figure 5, continued

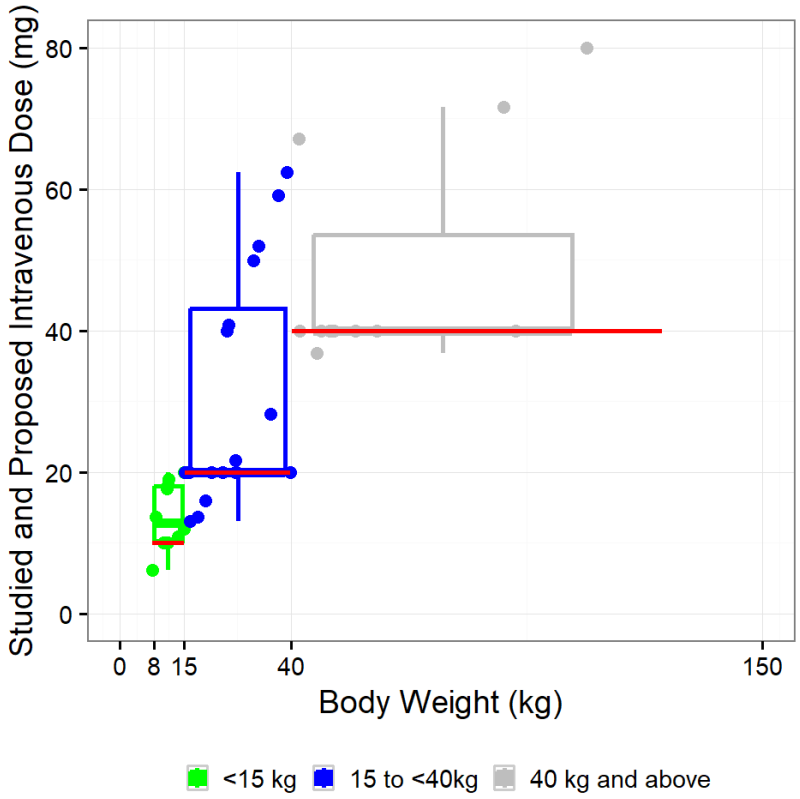


Source: Figure 1 and Figure 2 in Report PMAR-EQDD-B179a-sNDA-1294
Adult AUC and C_{max} values (n=55) were estimated by NCA from PK observations (from clinical studies) after a 40 mg IV dose. Dotted line corresponds to median adult exposure parameter. Boxes indicate the interquartile range with the median of the group shown by a horizontal black line. Whisker lines represent 1.5 times the interquartile range below the 1st or above the 3rd quartile. Black dots correspond to outlying points.
Abbreviation(s): AUC, area under the concentration-time curve; CL, clearance; C_{max}, maximum plasma drug concentration; IPRED, individual prediction; IV, intravenous

The Applicant's proposed dosing regimen in children 1 year and older for exposure matching to support efficacy extrapolation based on Figure 4 above is acceptable.

A comparison of the studied IV dose and Applicant-proposed IV dosing regimens is depicted in Figure 6 below. The studied dosing regimens in each BW cohort were either similar to or higher than the proposed dosing regimens. Therefore, the studied dosing regimens in children 1 year and older across the three BW cohorts provided adequate exposure coverage to support the safety evaluation for the proposed dosing regimens.

Figure 6. Comparison Between Studied and Proposed Intravenous Dosing Regimens in Children 1 Year and Older



Source: Reviewer's analysis
Solid dots: Studied dosing regimens
Boxplot: Studied dosing regimens
Red horizontal line: The Applicant-proposed dosing regimens

In infants <1 year old, no clinical study following IV administration was conducted. The Applicant relied on oral administration PK data in infants <1 year old and on both IV and oral administration PK data in children 1 year and older to extrapolate pantoprazole PK and to support the exposure assessment of IV pantoprazole PK in infants 1 to <12 months old. The reviewer's independent analysis on PopPK model-estimated bioavailabilities are given in Table 23. This approach assumed a same bioavailability between infants <1 year old and pediatric subjects 1 year and older.

Table 23. Population Pharmacokinetics Model Estimated Bioavailability in Different Age Cohorts

Age Range	Routes of Administration	Formulation	Bioavailability	Number of Subjects
<1 year	Oral	Spheroid	(36.5%)	116
	Intravenous	Injection		0
1 to 2 years	Oral	Spheroid	31.5%	5
	Intravenous	Injection		6
2 to 12 years	Oral	Spheroid	33.3% 63.5%	15 (2 to 6 yrs.) 1 (>6 yrs.)
	Oral	Tablet	135%	22 (>6 yrs.)
	Intravenous	Injection		11 (2 to 6 yrs.) 12 (>6 yrs.)

Age Range	Routes of Administration	Formulation	Bioavailability	Number of Subjects
12 years and older	Oral	Tablet	128%	21
	Intravenous	Injection		11

Source: Reviewer's analysis
Abbreviation(s): yrs, years

Two information requests were sent to the Applicant for clarification and additional justification for the assumed bioavailability in children 1 month to <1 year old. The Applicant responded to the information requests to justify the assumed bioavailability from both PK perspective and biopharmaceutical perspective:

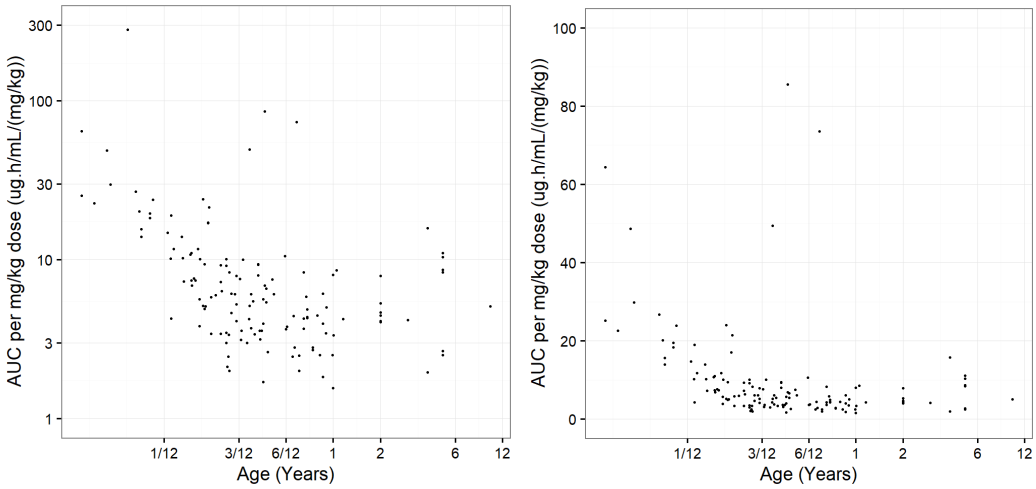
> The pantoprazole pediatric PopPK analysis used oral and IV pantoprazole PK data. Pediatric participants ≥1 year old had pantoprazole PK data following both oral and IV administration and thus joint Pop-PK analysis allowed adequate characterization of IV and oral PK and estimation of CL, Q, Vc and Vp which are independent of bioavailability. Pediatric participants <1 year old had PK data following oral administration only, therefore the PopPK model assumed the same bioavailability for pediatric participants <1 year old and ≥1 year old receiving the same pantoprazole formulation. This modeling approach integrated the available data (routes, formulations, and covariates across all age groups) to inform the estimation of CL (and other PK parameters) which were used for simulation of PK profiles following oral and IV routes of administration.
>
> The assumption of equivalent bioavailability between pediatric participants <1year old and ≥1 year old, for a given formulation, is supported by the **high oral bioavailability and low first-pass metabolism of pantoprazole, and the bioequivalence of oral pantoprazole granules and oral tablets**.
>
> The absolute oral bioavailability of pantoprazole in adults is approximately 77%, indicating that pantoprazole undergoes little first-pass metabolism and has almost complete absorption. Therefore, age-related differences in the expression of metabolic enzymes in the intestine and first pass metabolism will have minimal impact on pantoprazole absorption and oral bioavailability.
>
> The pantoprazole oral granules dosage form was designed for subjects who are unable to swallow a tablet. In pediatric PK studies, all 137 pediatric participants <6 years of age received oral granules. Out of those 137, 21 pediatric participants were >1 year old, and 116 participants were <1 year old. Relative bioavailability study (3001A1-114-US CSR-53163) of oral granules and tablets formulation in healthy adults showed that pantoprazole oral granules mixed with water or applesauce are bioequivalent with pantoprazole tablets for AUC(90% CI for geometric mean ratio within 80% to 125%) indicating no effect of formulation on pantoprazole bioavailability. C_{max} was approximately 34% to 38% lower for oral granules compared to oral tablets, which indicates slower absorption for granules compared to oral tablets. The lower C_{max} for oral granules formulation was anticipated based on in vivo release properties of the formulation. Both oral granules and tablets are enteric coated formulations. For the tablet formulation, the drug is released within a short time interval once the tablet reaches the small intestine after gastric emptying. However, for oral granules, some granules can be in the stomach and some in the small intestine, resulting from multiple waves of gastric emptying. Therefore, the absorption phase for the oral granules is longer than that for the tablets resulting in a lower C_{max} than for the tablets. However, the equivalent AUC supports similar overall absorption between these two formulations.

> Pantoprazole is extensively metabolized in the liver mainly by CYP2C19 (>80%) with minor contribution of CYP3A4 enzyme. We acknowledge that the metabolic CL of pantoprazole in infants <1 year old is lower than children ≥1 year old. To account for the effect of age on pantoprazole CL, age was added as a covariate on allometrically scaled CL by a sigmoid E_{max} model with the age effect reaching an asymptote approximately equal to the adult CL by 1 year. These results are consistent with published literature reports on ontogeny indicating that CYP2C19 expression (ontogeny) reaches the adult level by the age of 1 year. In summary, based on the high oral bioavailability and low first pass metabolism of pantoprazole, and the bioequivalence of oral granules and tablets, we believe that our assumption of similar pantoprazole bioavailability between infants <1 year old and children >1 year of age is appropriate.

The absolute bioavailability is 77% for the tablet formulation; however, the PopPK model estimated bioavailability is 135% in adults and 128% in adolescents per the reviewer's independent analysis. In a relative bioavailability conducted in healthy adult subjects, the observed relative bioavailability of spheroid formulation is 90% to the tablet formulation; however, the PopPK model-estimated relative bioavailability is 23% in infants and children per the reviewer's independent analysis. The reason for the discrepancies between the PopPK model-estimated bioavailability and bioavailability estimated in healthy adults remains unclear. Particularly, the PopPK model-estimated relative bioavailability of spheroid formulation of 23% is highly inconsistent with the 90% relative bioavailability observed in the dedicated PK study in healthy adult subjects.

The clinical pharmacology and pharmacometrics review team independently evaluated the potential of age-dependent CL and bioavailability in infants 1 month to <1 year old. Dose- and BW-adjusted AUCs were evaluated with age across 1 months to <12 years old (Figure 7).

Figure 7. Age-Dependent AUC Per Unit Dose (mg/kg) Following Oral Administration of Spheroid Formulation (Left: Log Scale; Right: Linear Scale)



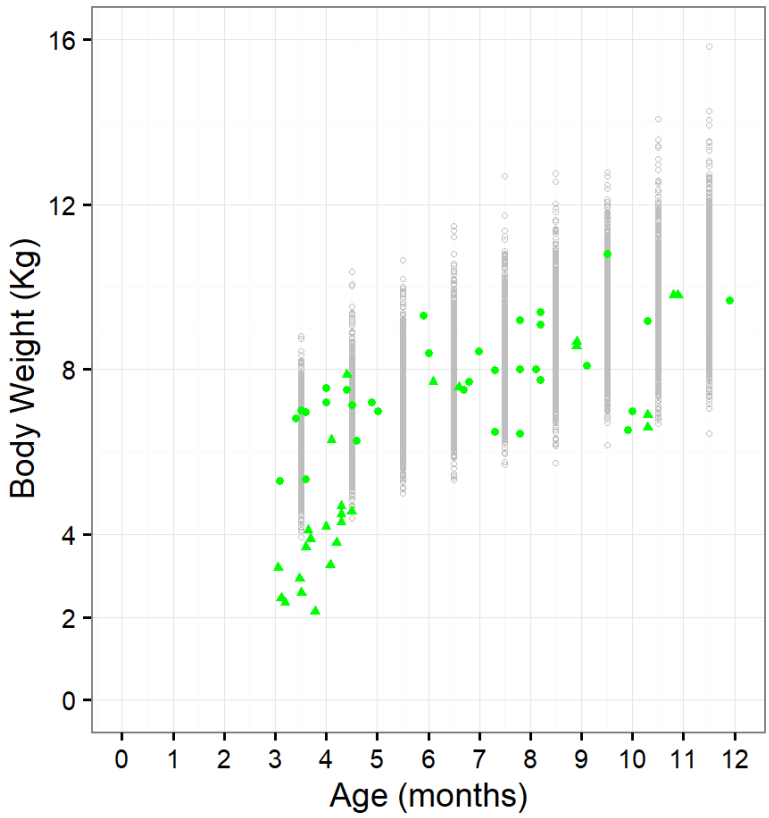
Source: Reviewer's analysis
Abbreviation(s): AUC, area under the concentration-time curve

Following a BW-adjusted oral dosing regimen (e.g., 1 mg/kg), AUC were not age dependent between 3 months old to 2 years old, which supported the bioavailability assumption in this age range. However, AUC was age dependent in infants <3 months old after dose and BW adjustment. Therefore, whether the bioavailability in infants <3 months is consistent with that in

older children remains unclear. Therefore, the Applicant-proposed dosing regimen of 0.8 mg/kg in infants 3 to <12 months old was further considered for exposure matching.

In the Applicant's simulation, BW distribution was resampled from the Centers for Disease Control and Prevention growth chart (hereafter refers to as virtual population). In comparison to the observed BW distribution in infants <12 months with GERD, the Applicant's simulated BW distribution was comparable to that of the full-term infants from the legacy studies (Figure 8). For exposure comparison purpose, the reviewer also conducted PK simulation based on posthoc estimates in full-term infants <12 months old (hereafter referred to as actual population) for exposure matching.

Figure 8. Distribution of Body Weight in the Applicant's Simulated Virtual Population and Actual Population (Infants 3 Months to <1 Year Old)



Source: Reviewer's analysis
Solid green dots: observed body weight in pantoprazole full term infants
Solid green triangles: observed body weight in pantoprazole preterm infants
Open grey dots: body weight resampled from CDC growth chart by the Applicant

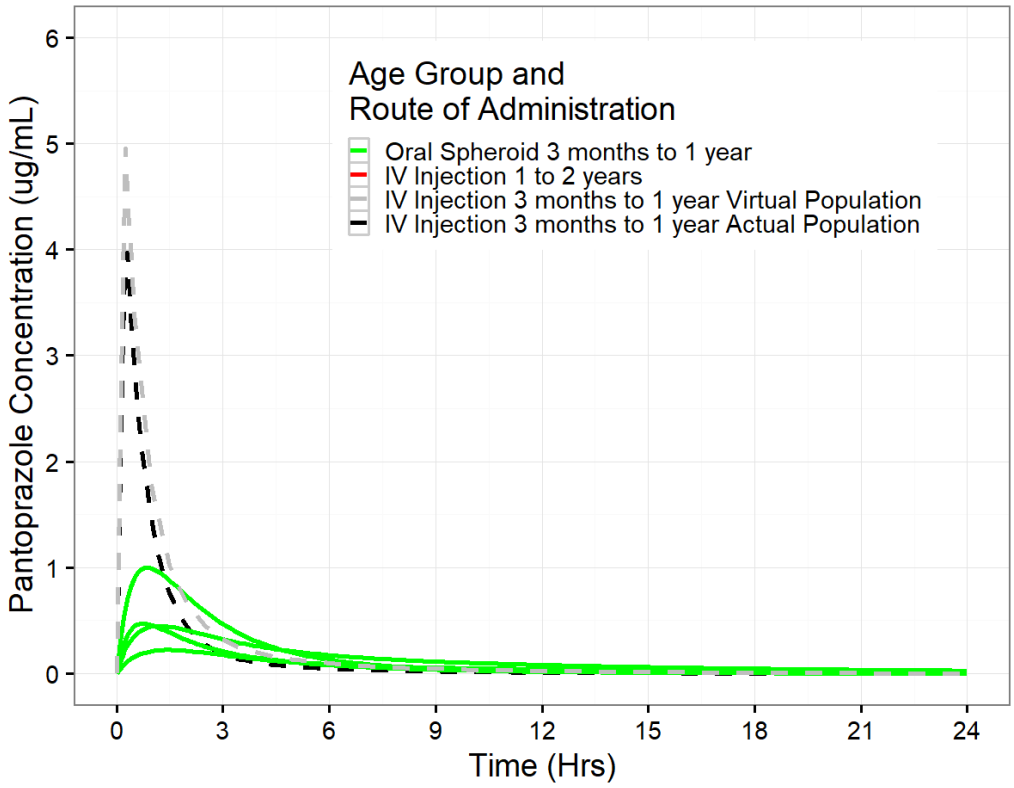
The Applicant-proposed dosing regimen of 0.8 mg/kg (maximum dose of 10 mg) in infants 3 to <12 months old showed similar AUC compared to adults (40 mg IV) for efficacy extrapolation and to infants (10 mg oral) for safety evaluation. C_{max} was higher than the observed C_{max} in infants <12 months old following oral administration but was similar to the observed C_{max} in children 1 to <2 years old following IV administration (see Table 24 and Figures Figure 9 to Figure 11). See Section 7.7.1.

Table 24. Statistical Summary of PK Parameters

Population	Dose	N	AUC (µg.h/mL)	C_{max} (µg/mL)
Predicted 3 to <12 months IV (virtual population)	0.8 mg/kg		5.0±3.4	6.3±3.2
Predicted 3 to <12 months IV (actual population)	0.8 mg/kg	29[a]	4.0±1.8	4.0±0.68
Observed 3 to <12 months oral	1.25 mg	4	1.2±0.61	0.23±0.10
	2.5 mg	10[b]	3.1±6.6	0.49±0.57
	5 mg	29[c]	2.1±3.1	0.53±0.39
	10 mg	12	3.4±2.5	1.1±0.78
Observed 1 to <2 years IV	Combined (11.4 mg)	6	4.6±2.4	5.7±1.6
	10 mg	2		
	0.8 mg/kg	2		
	1.6 mg/kg	2		
Observed 1 to <2 years oral	Combined (9 mg)	5	2.5±2.6	0.59±0.75
	5 mg	2		
	10 mg	2		
	15 mg	1		
Adults IV	40 mg	55	6.02±4.18	6.26±3.01

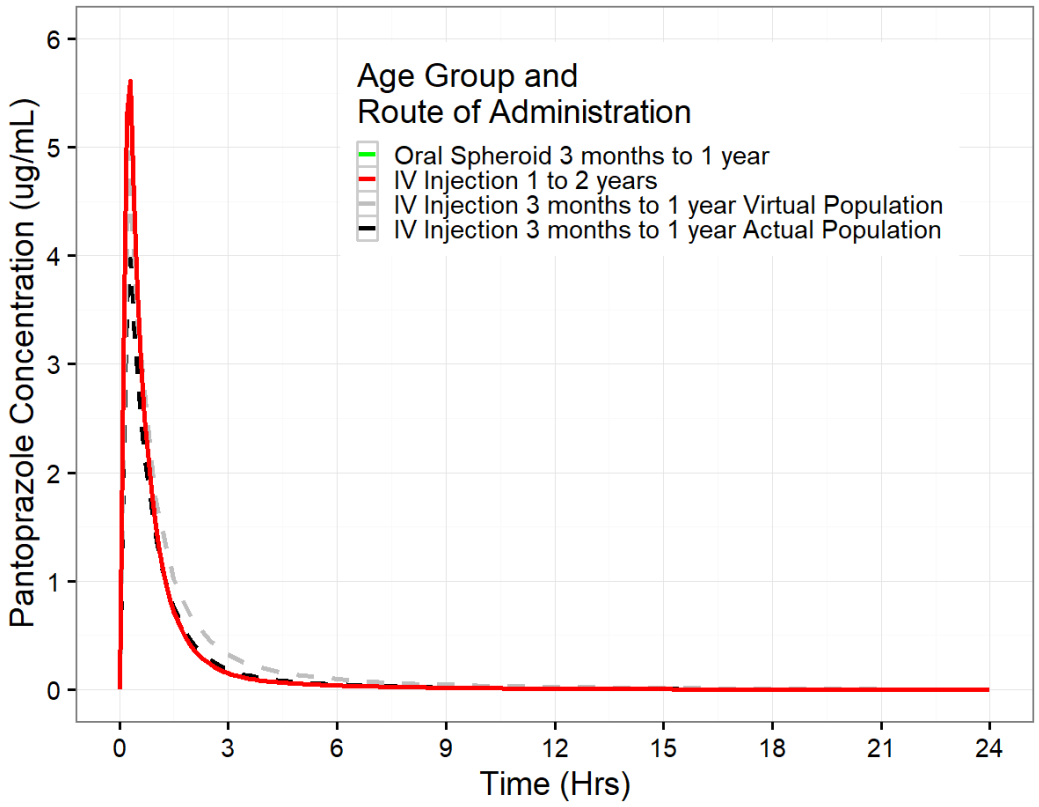
Source: reviewer's analysis
[a] Exclude 3 poor metabolizers and 26 preterm infants
[b] Include 1 poor metabolizer
[c] Include 2 poor metabolizers
Abbreviation(s): AUC, area under the concentration-time curve; C_{max}, peak serum drug concentration; IV, intravenous; N, number of subjects; PK, pharmacokinetic

Figure 9. Concentration Time Profiles of Pantoprazole in Infants 3 to <12 Months Old Following IV Administration (0.8 mg/kg With Maximum Dose of 10 mg) and Oral Administration of Studied Dosing Regimen (1.25 mg, 2.5 mg, 5 mg, and 10 mg)



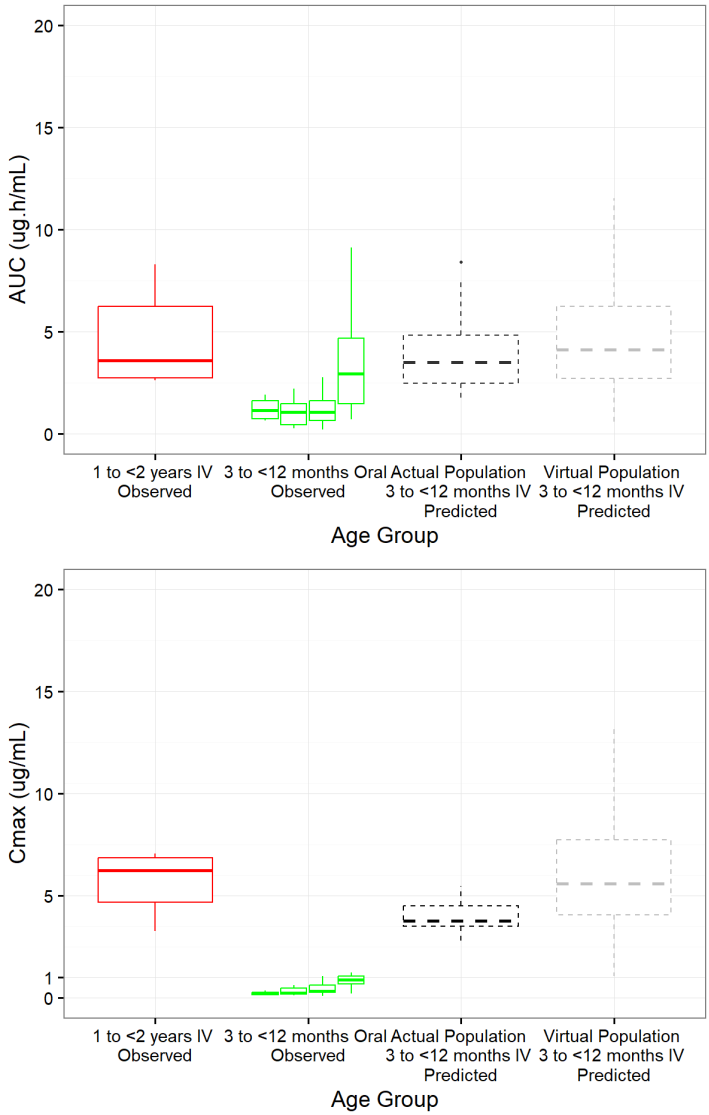
Source: Reviewer's analysis
Abbreviation(s): hrs, hours; IV, intravenous

Figure 10. Concentration Time Profiles of Pantoprazole in Infants 3 to <12 Months Old Following IV Administration (0.8 mg/kg With Maximum Dose of 10 mg) and Children 1 to <2 Years Old Following the Studied IV Regimen (N=6, Average Dose 11.4 mg)



Source: Reviewer's analysis
Abbreviation(s): hrs, hours; IV, intravenous; N, number of subjects

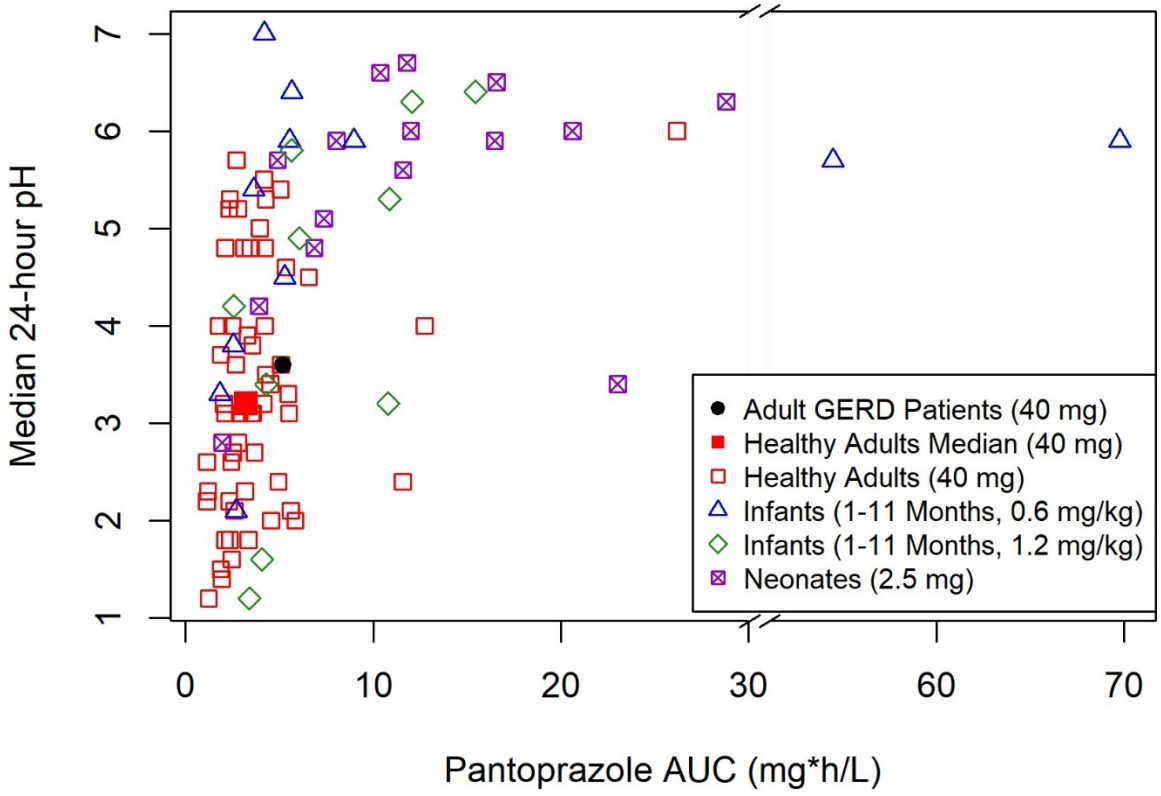
Figure 11. Comparison of AUC and C_{max} in Infants 3 to <12 Months Old Following IV Administration (0.8 mg/kg With Maximum Dose of 10 mg) and Children 1 to <2 Years Old Following the Studied IV Regimen (N=6, Average Dose 11.4 mg)



Source: Reviewer's analysis
Abbreviation(s): AUC, area under the concentration-time curve; C_{max}, peak serum drug concentration; IV, intravenous; N, number of subjects

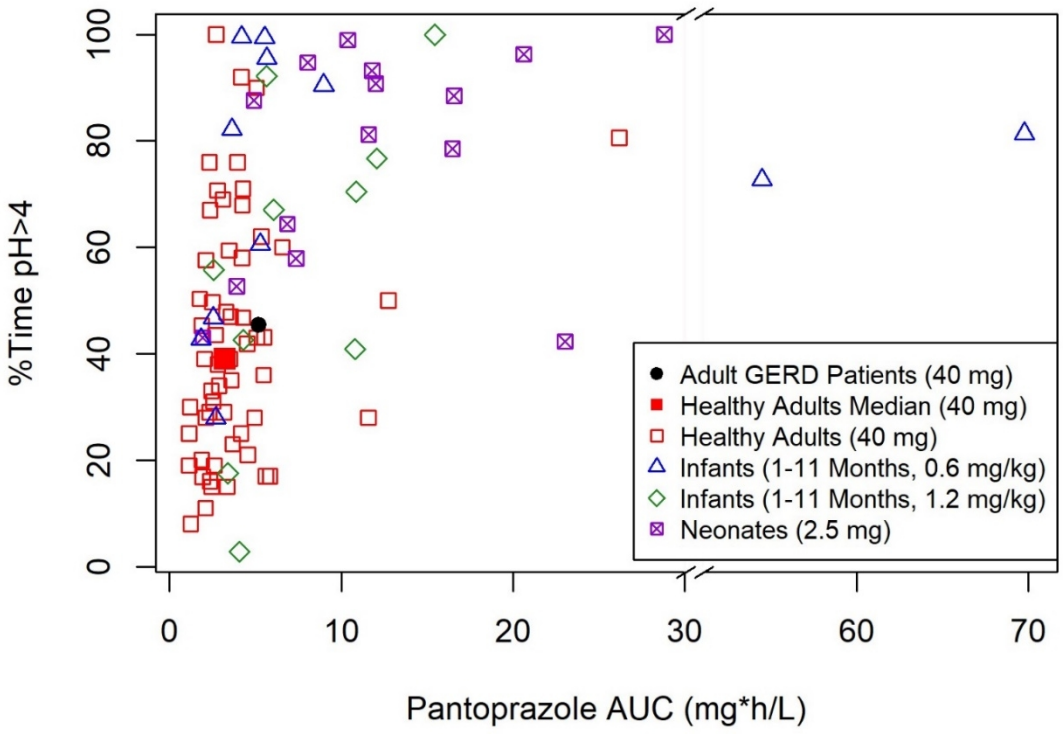
To support the efficacy extrapolation in infants <1 year of age with GERD associated with EE, the Applicant compared pantoprazole exposure-response relationships following single and multiple oral dosing in neonates, infants, and IV/oral dosing in adults. Figures Figure 12 and Figure 13 present the median 24-hour intragastric pH versus oral pantoprazole exposure (AUC) and % time intragastric pH above 4 versus oral pantoprazole exposure (AUC), respectively, following multiple doses (once daily dosing for 5 to 7 days) in neonates, infants, and adults.

Figure 12. Median 24-Hour Intragastric pH Versus Pantoprazole Exposure (AUC) Following Multiple Dosing in Neonates, Infants and Adults



Source: Figure 1 in Report PMAR-EQDD-B179a-sNDA-1623
Abbreviation(s): AUC, area under the concentration-time curve; GERD, gastroesophageal reflux disease

Figure 13. Percent Time Intragastric pH >4 Versus Pantoprazole Exposure (AUC) Following Multiple Dosing in Neonates, Infants and Adults



Source: Figure 2 in Report PMAR-EQDD-B179a-sNDA-1623
Abbreviation(s): AUC, area under the concentration-time curve; GERD, gastroesophageal reflux disease

The exposure-response relationships (median 24-hour intragastric pH and % time pH >4.0) are reasonably overlapping between the adult and infants <1 year old. These data supported the efficacy extrapolation from adults to infants <1 year old with GERD associated with EE.

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

The study design and endpoints for the newly conducted studies submitted to this efficacy supplement are summarized below.

15.1. Study B1791089

A nonrandomized, open-label, multicenter study to evaluate the PK of single and multiple IV doses of pantoprazole in two age cohorts of hospitalized pediatric subjects 1 to 16 years of age who were candidates for acid suppression therapy.

Study Objectives and Endpoints

The primary objective was to characterize the PK of pantoprazole sodium following single and multiple IV doses in pediatric subjects 1 to <2 years of age and in subjects 2 to 16 year of age. The primary endpoints were CL and volume of distribution. The secondary objective was to evaluate the safety, tolerability, and PK of single and multiple IV doses of pantoprazole sodium in each of the two age cohorts. The secondary endpoints accordingly were PK parameters of C_{max}, AUC_{24}, AUC_{inf}, and $T_{1/2}$ estimated using the population PK model and the safety and tolerability of single and multiple doses of IV pantoprazole sodium for each of the two age cohorts as assessed by physical examinations, adverse event (AE) monitoring, clinical laboratory measurements, blood pressure, and pulse rate. Additionally, the genotype of CYP2C19, the major enzyme responsible for the metabolism of pantoprazole, was evaluated in this study.

Inclusion Criteria

The primary inclusion criterion for this study included subjects aged 1 to 16 years who, in the judgment of the investigator, were candidates for gastric acid suppression therapy (i.e., those with a presumptive diagnosis of GERD, a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD) and whom the investigator judged would need to receive IV proton pump inhibitor therapy for at least 4 days. Subjects were to have a physical examination and laboratory evaluations within normal limits unless deviations were deemed by the investigator as not clinically significant or as directly related to the gastric acid suppression therapy or underlying disease process. Subjects were to have a BW >5th percentile for their age.

Exclusion Criteria

Subjects with any of the following characteristics/conditions were not included in the study:

1. Subjects who were investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees directly involved in the conduct of the trial.
2. Participation in other studies involving investigational drug(s) within 30 days or 5 half-lives prior to study entry and/or during study participation.
3. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
4. Pregnant females, breastfeeding females, fertile male subjects, and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product.
5. Serum creatine kinase levels >3 times the upper limit of normal.
6. Known history of HIV or clinical manifestations of AIDS.
7. Known hypersensitivity to proton pump inhibitors, including pantoprazole sodium or any substituted benzimidazole, or to any of the excipients.

8. History of treatment with any proton pump inhibitor (e.g., omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole sodium) within 2 days (i.e., 48 hours) before investigational product dosing on day 1.
9. Use of histamine-2 receptor blockers (e.g., cimetidine, famotidine, ranitidine, nizatidine), sucralfate, misoprostol, or prokinetic agents (e.g., cisapride, urecholine, erythromycin, metoclopramide), and bismuth preparations within 1 day (i.e., 24 hours) before investigational product dosing on day 1, whether prescription or over the counter.
10. Any disorder requiring chronic (every day) use of warfarin, carbamazepine or phenytoin, methotrexate, atazanavir or nelfinavir, clopidogrel, and potent inhibitors and inducers of CYP2C19.
11. Chronic (daily) use of glucocorticoids (e.g., prednisone, prednisolone, dexamethasone). Steroid inhalers and topical steroids may be used.
12. Active malignancy of any type or history of a malignancy (subjects with a history of malignancies that have been surgically removed or eradicated by irradiation or chemotherapy and who have no evidence of recurrence for at least 5 years before screening are acceptable).
13. Alanine aminotransferase or blood urea nitrogen >2 times the upper limit of normal or estimated creatinine >1.5 times the upper limit of normal for age or any other laboratory abnormality considered by the investigator to be clinically significant within 14 days before screening.
14. In the investigator's opinion, a chronic condition (e.g., diabetes, epilepsy), which is either not stable or well controlled and may interfere with the conduct of the study.
15. History of sensitivity to heparin or heparin-induced thrombocytopenia.

Study Conduct

The study was conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects,[22] International Council for Harmonisation Guideline for Good Clinical Practices (1996), and the Declaration of Helsinki.

Sample Size

The study planned to enroll 12 subjects in each of the two age cohorts. This was estimated using simulations of a previous population PK model of pantoprazole in pediatric patients reported by Knebel et al.[23] and was deemed likely to have an 80% chance to achieve 20% relative standard error for both CL and volume of distribution. Overall, 19 subjects were enrolled (3 in the 1 to 2 years age cohort and 16 in the 2 to 16 years age cohort, with approximate equal distribution across the subcohorts of 2 to 5, 6 to 11, and 12 to 16 years), and 18 received the study intervention and completed the study. Consent was withdrawn for one subject (b) (6) in the

[22] Council for International Organizations of Medical Sciences, 2002, International Ethical Guidelines for Biomedical Research Involving Human Subjects, Bull Med Ethics, 182:17-23

[23] W Knebel, B Tammara, C Udata, G Comer, M Gastonguay, X Meng, 2011, Population Pharmacokinetic Modeling of Pantoprazole in Pediatric Patients From Birth to 16 Years, J Clin Pharmacol, 51(3):333-345

1 to 2 years cohort prior to being administered the study intervention. One subject in the 2 to 16 years cohort had a diagnosis of EE. The remaining had GERD.

Dosing and Administration

Pantoprazole sodium was administered intravenously over 15 minutes through a Y-site or dedicated IV line once daily for 4 to 7 days approximately every 24 hours, preferably in the morning. Subjects received a fixed dose of IV pantoprazole sodium according to their BW:

- BW <15 kg: 10 mg
- BW 15 to <40 kg: 20 mg
- BW ≥40 kg: 40 mg

The maximum dose in the study did not exceed 40 mg. Pantoprazole 40 mg lyophilized drug product from six different Pfizer lots were used in this study.

PK Sampling

Blood sampling for PK analysis of pantoprazole was obtained on day 1 (at 0.25, 1 to 2, 3 to 4, and 5 to 6 hours after the start of the infusion) and on day 2 (predose and at 0.25, 1 to 2, 3 to 4, and 5 to 6 hours after the start of the infusion).

Safety Analysis

Study evaluated and collected safety laboratory data and data regarding AEs, physical examinations, blood pressure, and pulse rate on an ongoing basis. Data on treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), discontinuations due to AEs, severity and causality assessments, exposure during pregnancy, hospitalization, potential cases of drug induced liver injury etc., were collected.

Protocol Amendments

The original protocol dated March 27, 2014, was amended three times. After enrolling 16 subjects in the 2 to 16 years age cohort, and 2 in the 1 to <2 years age cohort, the study was terminated prematurely with FDA agreement due to difficult enrolling into the younger age cohort and the length of time it might take to achieve the target enrollment of 12 subjects. Major changes to the protocol are summarized in Table 25 below.

Table 25. Summary of Protocol Amendments, Study B1791089

Amendment	Date	Summary of Changes
1.0	October 28, 2014	• Changed compound number from PF-00579917 to PF-05208751 and protocol number from B2851006 to B1791089. • Removed 1 to 11 months cohort in agreement with FDA. • Updated exclusion criteria to indicate that screening endoscopy was not required. • Removed ECG and exclusion criteria related to QT prolongation, elevation of AST. • Changed investigational product dosing in response to FDA request. • Specified that PK samples were to be collected from the IV line. • Added daily vital signs.
2.0	June 29, 2017	• Reduced PPI and H2RA washout periods, removed exclusion criteria for upper GI abnormalities and treatment for GI ulcers. • Updated the diagnosis of GERD in young children, collection of PK samples, and collection of temperature. • Added ECG or rhythm strip to document if a pulse rate abnormality was detected.
3.0	November 7, 2018	• Updated PK sampling: 9 samples total (4 samples on Day 1 and 5 samples on Day 2) for all age cohorts to make the study feasible. • Updated treatment duration, depending on subject need (4-7 days), to make the study more feasible. • Physical examination and safety laboratory assessments were moved to the day after the last dose to ensure all evaluations were done after treatment was completed. Assessments of vital signs, AEs, and concomitant medications were extended to include the day after the last dose.

Source: Reviewer-generated table using protocol amendment information for Study B1791089 (NDA 20988/s-070; Module 5.3.5.1).
Abbreviation(s): AE, adverse events; AST, aspartate aminotransferase; ECG, electrocardiogram; GERD, gastroesophageal reflux disease; GI, gastrointestinal; H2RA, histamine-2 receptor antagonist; IV, intravenous; PK, pharmacokinetic; PPI, proton pump inhibitor

Table 26. Schedule of Activities

Protocol Activity	Screening	Treatment Period			Day After Last Dose	Follow- Up 31 (±3) Days After Last Dose
	Day 0 or Day 1 Prior to Treatment	Day 1	Day 2	-Daily During Treatment		
Subject/parent/legal guardian informed consent	X					
Review Inclusion/Exclusion	X					
Medical history[a]	X					
Physical examination[b]	X				X	
Vital Signs[c]	X	X	X	X	X	
Safety Laboratory evaluation[d]	X				X[h]	
Pregnancy test[e]	X				X	
Subject Enrollment		X				
Investigational product administration[f]		X	X	X		
PK blood sample collection[g]		X	X			
Pharmacogenomics (Buccal cell collection for CYP2C19 genotyping)		X				
Drug Accountability		X	X	X		
Prior/Concomitant Medication	X	→	→	→	X	X
Telephone contact						X
Adverse Event Monitoring	X	→	→	→	X	X

a. Medical history includes complete history of all prescription or nonprescription drugs, vitamins, and dietary supplements taken prior to screening procedures, history of drug, alcohol, and tobacco use.

b. Physical exam will include height (cm) (Screening only) and weight (kg).

c. Blood pressure, pulse rate, and temperature (C°). Every effort should be made to collect blood pressure at approximately the same time each day. If a pulse rate abnormality is detected, ECG or rhythm strip should be obtained to document this.

d. Refer to ASSESSMENTS sectionfor a list of laboratory parameters.

e. For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, within 24 hours before investigational product administration. On the day after the last dose a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

f. Refer to the Preparation and Dispensing section of this protocol and IP Manual, which is provided separately.

g. Refer to the Pharmacokinetics section of this protocol for PK collection times.

h. To minimize the amount of blood collected, routine laboratory studies planned within 48 hours after the last dose of investigational product may be used as the final study evaluation safety laboratory values, provided the information specified in the protocol is obtained.

Source: Protocol B1791089 Amendment 3

Safety findings are discussed in Section 7.6. Subject characteristics are summarized below.

Table 27. Baseline Demographics and Clinical Characteristics, Safety Population, Study B1791089

Characteristic	Cohort 1 (1 to <2 Years) N=2	Cohort 2 (2 to 16 Years) N=16	Total N=18
Sex, n (%)			
Female	0	7 (43.8)	7 (38.9)
Male	2 (100)	9 (56.2)	11 (61.1)
Age, years			
Mean (SD)	1 (0)	9.3 (4.7)	8.4 (5.2)
Median (min, max)	1 (1, 1)	9 (3, 16)	9 (1, 16)

Characteristic	Cohort 1 (1 to <2 Years) N=2	Cohort 2 (2 to 16 Years) N=16	Total N=18
Age group, years, n (%)			
≥1 to <2	2 (100)	0	2 (11.1)
≥2 to <5	0	5 (31.2)	5 (27.8)
≥5 to <11	0	5 (31.2)	5 (27.8)
≥11 to <17	0	6 (37.5)	6 (33.3)
Race, n (%)			
White	2 (100)	16 (100)	18 (100)
Ethnicity, n (%)			
Not Hispanic or Latino	2 (100)	16 (100)	18 (100)
Country of participation, n (%)			
Bosnia and Herzegovina	0	1 (6.2)	1 (5.6)
Germany	0	3 (18.8)	3 (16.7)
Georgia	1 (50.0)	7 (43.8)	8 (44.4)
Italy	0	3 (18.8)	3 (16.7)
Slovakia	1 (50.0)	2 (12.5)	3 (16.7)
Is in United States, n (%)			
Non-United States	2 (100)	16 (100)	18 (100)

Source: CDS-generated; adsl.xpt; Software: R
Abbreviation(s): N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Table 28. Subject Screening and Enrollment, Study B1791089

Disposition	Trial B1791089
Subjects screened	20
Screening failures	0
Subjects enrolled	19
Subjects randomized	19

Source: CDS-generated; ds.xpt and Clinical Study Report; Software: R

Table 29. Subject Disposition, Study B1791089

Disposition Outcome	Cohort 1 (1 to <2 Years) N=2 n (%)	Cohort 2 (2 to 16 Years) N=16 n (%)	Total N=18 n (%)
Subjects randomized	3	16	19
Safety population	2	16	18
Discontinued study drug	0	0	0
Discontinued study	0	0	0

Source: CDS-generated; ds.xpt and adsl.xpt; Software: R
Duration is 4 to 7 days.
Abbreviation(s): n, number of subjects in specified population or group; N, number of subjects in treatment arm

15.2. Study B1791096

"A Real-World Study Evaluating the Safety of Pantoprazole Sodium IV in Infants Aged 1 Month to <1 Year and Patients Aged 1 to <2 Years Using an Electronic Health Records (EHR) Database from the United States."

This noninterventional study was voluntarily conducted by the Applicant to collect safety data in two separate cohorts of infants aged 1 month to <1 year and patients aged 1 to <2 years who were treated with IV pantoprazole, with a primary focus on patients with a diagnosis of GERD

with or without EE using an EHR database from the United States. This study was done in lieu of the originally proposed case series study in infants as this age group was not enrolled into the prospective PK and safety study B1791089.

Study Design

This was a single-arm (uncontrolled), retrospective, observational study using healthcare data assembled from EHR linked to health insurance claims in the United States.

Research Question

The study attempted to address the following questions: What are the incidence rates (IRs) of potential safety events of interest in infants aged 1 month to <1 year and in patients aged 1 to <2 years who were treated with IV pantoprazole in the real-world setting?

Data Source

(b) (4) longitudinal EHR repository from the United States was used for this study to identify patients <2 years of age who received IV pantoprazole at least once during a 14-year period from January 1, 2007, through December 31, 2020.

Study Population

All eligible subjects meeting the inclusion and exclusion criteria were included in the study. International Classification of Diseases (ICD), ninth or tenth revisions, Clinical Modification (CM) was used to identify patients (ICD-9-CM, or ICD-10-CM). Within each age cohort, codes for the following three subgroups were identified as patients who have a diagnosis of 1) GERD with EE, 2) GERD without EE, and 3) without GERD or EE. ICD-9-CM codes were used to identify the subgroups prior to October 2015, after which ICD-10-CM codes were used. B1791096 identified no infants with diagnostic coding for EE.

Inclusion Criteria

Subjects must have met all the inclusion criteria to be eligible for the study:

1. At least one administration of IV pantoprazole during the study period from January 1, 2007, to December 31, 2020.
2. For the cohort of infants aged 1 month to <1 year (Cohort 1): Age 1 month to <1 year on the index date (i.e., the date of first administration of IV pantoprazole); for the cohort of subjects aged 1 to <2 years (Cohort 2): Age 1 to <2 years on the index date.
3. Subjects must be enrolled in the database for at least 30 days prior to the index date.

Exclusion Criteria

Subjects with any of the ICD-9-CM or ICD-10-CM codes occurring prior to or on the index date indicating a preterm birth or birth weight <2.36 kg were excluded.

Sample Size

Given that there were no a priori hypotheses specified, sample size calculations were not applicable and all eligible subjects meeting inclusion and exclusion criteria were included.

Overall, 1,879 infants (Cohort 1) and 981 subjects 1 to <2 years (Cohort 2) met the inclusion and exclusion criteria. There were no subjects with a diagnosis of EE in either age cohorts.

Objectives and Endpoints

Main analyses estimated 90-day incidence for 25 safety outcomes of interest in the two cohorts (1 to <12 months and 1 to <2 years) with ≥30 days of pretreatment database coverage and pretreatment diagnostic coding for GERD. Within each of the two age cohorts, the following primary and secondary objectives were assessed.

Primary Objective

To estimate the incidence of prespecified outcomes of interest listed below in subjects with a diagnosis of GERD with or without EE and treated with IV pantoprazole. Per the Applicant, the outcomes of interest were based on the Investigator's Brochure (version 4.0 June 2021) and expert clinical judgment:

> Agranulocytosis, thrombocytopenia, leukopenia, pancytopenia, hypersensitivity (including anaphylactic reactions and anaphylactic shock), hyperlipidaemia, hypertriglyceridemia, hyponatraemia, hypomagnesaemia, hypocalcaemia, hypokalaemia, diarrhea, vomiting, abdominal distension, hepatobiliary injury, urticaria, angioedema, Stevens-Johnson syndrome, Lyell syndrome *[Toxic Epidermal Necrolysis]*, erythema multiforme, drug rash with eosinophilia and systemic symptoms, tubulointerstitial nephritis, photosensitivity, peripheral edema and injection site thrombophlebitis.

Secondary Objectives

1. To estimate the incidence of prespecified outcomes of interest in subjects treated with IV pantoprazole without a diagnosis of GERD or EE
2. To provide the frequency of the 25 most common diagnostic codes occurring within 30 days prior to or on the date of initiation of IV pantoprazole through 90 days of the last treatment with IV pantoprazole in subjects with a diagnosis of GERD (regardless of EE diagnosis)

The other key variables of interest included demographic characteristics, comorbidities, duration, and dose of IV pantoprazole.

Exposure Ascertainment

Exposure to IV pantoprazole was identified from inpatient procedure and drug codes, including National Drug Codes (NDC) and Healthcare Common Procedure Coding System codes. The date of first administration of IV pantoprazole was defined as the index date. For each outcome, subjects were followed from the index date to whichever of the following occurred first: occurrence of the prespecified outcome of interest, 90 days following the last date of IV pantoprazole administration, initiation of a separate IV pantoprazole infusion within 90 days following the discontinuation of IV pantoprazole administration, death, end of enrollment in the database, or end of study period (i.e., 31 December 2020). Only the first treatment episode during the study period was of interest.

Study Conduct

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor, and followed generally accepted research practices described in the FDA guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005),[24] Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology,[25] and FDA guidance for industry and FDA staff *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* (May 2013).[26]

Dosing Information

Duration of IV pantoprazole in days was ascertained as follows: Date of last infusion during the observation period – date of first infusion during the observation period plus 1 day (minus treatment gaps, defined as a date with no record of infusion between the date of last infusion and date of first infusion; up to 7 days treatment gap between infusions was allowed). Total daily dose of IV pantoprazole was reported in mg/kg/day.

Data Analysis

Deidentified (b) (4) EHR data were analyzed using a data handling tool. Within each age group of interest, descriptive statistics were presented for the key variables of interest in the overall age cohort and across the subgroups based on baseline disease. These included counts and percentages for categorical data and statistics, such as mean, median, standard deviation, and range for continuous variables. The IR for outcomes of interest was restricted to subjects without the outcome prior to the index date, i.e., during the baseline period and estimated as the number of subjects with a specific outcome of interest during the follow-up period divided by the total person-time at risk and reported as IR per 1,000 person-years with associated 95% CIs. Incidence rates were also estimated by the duration of IV pantoprazole treatment (<4 days, ≥4 days). Sensitivity analyses were performed without the minimum 30-day enrollment period prior to the index date and by stratification of subject identification via ICD-9-CM versus ICD-10-CM codes.

As indicated by the Applicant, limitations of the study include the following:

- Potential for missing a diagnosis of EE: Infants with a diagnosis of GERD with EE may be misclassified as those without EE. This is because a confirmed diagnosis of GERD with EE may not be available in infants due to reluctance of healthcare professionals to seek a confirmation via endoscopy. Also, those with a presumptive diagnosis of EE may be classified into the subset of infants with GERD alone. Prior to October 2015, ICD-9-CM codes were exclusively used to identify eligible patients, and GERD is not explicitly captured

[24] See the guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005) (https://www.fda.gov/media/71546/download).

[25] International Society for Pharmacoepidemiology, 2008, Guidelines for Good Pharmacoepidemiology Practices, 17(2):200-208.

[26] See the guidance for industry and FDA staff *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* (May 2013) (https://www.fda.gov/media/79922/download).

under this coding schema. ICD-10-CM codes provide additional granularity, but a validated code for EE and GERD is not available, well-established, or validated in the literature.

- Potential for outcome misclassification or under-reporting: Diagnosis codes may be incorrect or may be included as part of the diagnostic rule-out process rather than an indication of diagnosis itself. Conditions not requiring treatment or office visits tend to be systematically under coded in such databases. It is possible that this study will only capture severe manifestations of such disorders.
- Approximation of subject age: The Applicant noted that only birth year was available in (b) (4). Therefore, age on the index date was calculated using the subject's birth year and data on insurance enrollment or medical activity in the database. Birth date was approximated to whichever of the following occurred first during the subject's birth year: date of insurance enrollment, date of first medical activity, or if neither dates were available in the database, the birth date was defaulted to June 30th of the birth year.
- Inadequate dosing information: The Applicant noted that the actual administered dose was unknown, as a dose variable does not exist in the (b) (4) dataset. However, an Ingredient Strength variable was generated using the strength from the NDC codes, and the dose was calculated by dividing the strength from the NDC code (counted on each day with an NDC code recorded) by the duration of the inpatient stay. It should be noted that all NDC codes had a strength of 40 mg. Subjects were only included in the dose calculation if they had a separate IV pantoprazole strength unit recorded.

Safety findings are summarized in Section 7.6. Subject characteristics and duration of exposure are summarized below. For further details, defer to DEPI review of Study B1791096, dated February 15, 2024.

Table 30. Baseline Demographics and Clinical Characteristics, Safety Population, Study B1791096

	Age 1 month to <1 year		Age 1 year to <2 years	
Baseline Characteristic	**GERD N=851**	**No GERD N=1,028**	**GERD N=462**	**No GERD N=519**
Age, weeks, mean (SD)	22.7 (13.2)	21.8 (14.3)	74.0 (14.9)	76.4 (15.3)
Sex, female, n (%)	361 (42.4)	445 (43.3)	206 (44.6)	224 (43.2)
H2RA, n (%)	609 (71.6)	545 (53.0)	360 (77.9)	241 (46.4)
PPI, n (%)	317 (37.3)	168 (16.3)	273 (59.1)	113 (21.8)
Weight (See **FOOTNOTE**)				
missing value, n (%)	276 (32.4)	468 (45.5)	152 (32.9)	229 (44.1)
non-missing value, n (%)	575 (67.6)	560 (54.5)	310 (67.1)	290 (55.9)
median, kg	5.7	5.5	9.7	10.5
IQR, kg	4.4-7.2	4.0-7.4	8.6-10.9	9.0-11.8
range, kg	2.5-16.2	1.9-13.6	4.5-20.3	1.5-17.0

Source: DEPI review of Study B1791096, DARRTs; 02/15/2024
Abbreviation(s): GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; IQR, interquartile range; N, number of subjects in each group; PPI, proton pump inhibitor; SD, standard deviation

Table 31. Duration of Exposure, Safety Population, Study B1791096

	Age 1 Month to <1 Year		Age 1 Year to <2 Years	
Duration of IV Pantoprazole	**GERD N=851**	**No GERD N=1,028**	**GERD N=462**	**No GERD N=519**
1 day	211 (24.8)	241 (23.4)	139 (30.1)	146 (28.1)
2-3 days	262 (30.8)	301 (29.3)	152 (32.9)	153 (29.5)
4-7 days	209 (24.6)	217 (21.1)	98 (21.2)	116 (22.4)
>7 days	169 (19.9)	269 (26.2)	73 (15.8)	104 (20.0)

Source: DEPI Review in DARRTs; 02/15/2024
Abbreviation(s): GERD, gastroesophageal reflux disease; IV, intravenous; N, number of subjects in each group

16. Efficacy

Efficacy trials were not conducted for this pediatric supplement.

17. Clinical Safety

17.1. Safety Summary From Legacy Wyeth Studies in Pediatric Patients

The Applicant included pediatric studies using either oral Protonix granules or tablets or IV dosing that were previously submitted and reviewed under NDA 22020/S-001 and S-002. Studies were not reviewed in detail again. Reference is made to the approved labeling for Protonix and Protonix IV and to the clinical review of oral Protonix pediatric supplemental NDAs 22020/20987 (Sequence # 020) finalized in DARRTs on August 10, 2009. Approval of these supplements provided for the use of PROTONIX (pantoprazole sodium) for Delayed-Release Oral Suspension 40 mg (NDA 22020/S-002), and PROTONIX (pantoprazole sodium) Delayed-Release Tablet, 20 mg and 40 mg (NDA 20987/S-036 and S-037) for the short-term treatment of erosive esophagitis associated with GERD in pediatric patients ages five years and older. The applications also provide for revisions to the package insert to include clinical and pharmacokinetic data from studies in pediatric patients birth through five years of age.

Regarding the legacy IV pantoprazole studies 3001K1-110-US, and 3001K1-117-US in pediatric subjects, clinical reviewer noted in their review dated August 10, 2009, that the safety data from these studies was reviewed; however, as there were no concerning safety signals a written review was not included. Therefore, relevant safety data from these two studies is provided below based on the legacy reports submitted to NDA 20988/S-070:

17.1.1. Additional Safety Information From the Legacy Pediatric IV Studies

Studies 3001K1-117-US and 3001K1-110-US evaluated the PK, pharmacodynamic, and safety of single IV doses of pantoprazole 0.8 mg/kg or 1.6 mg/kg infused over 15 minutes in hospitalized pediatric subjects 1 to <2 years of age (N=4) and 2 to 16 years (N=19), respectively.

Study 3001K1-117-US enrolled four subjects (two males and two females; 12 months to 17 months of age; two Black and two White). All were extensive metabolizers of CYP2C19. Two

subjects were diagnosed with gastrointestinal reflux, one had diarrhea and vomiting, and one had a normal gastrointestinal function at study entry.

There were no TEAEs during the single IV dose treatment period. During the 15-day follow up period, 2 of the 4 subjects had TEAEs.

- Subject (b) (6) (14 months of age, female, Black; 0.8 mg/kg single IV pantoprazole dose; 6.1 mg): The subject was hospitalized on (b) (6), for the treatment of dehydration, vomiting, and diarrhea, and received 0.8 mg/kg IV dose (5.76 mg) of pantoprazole on (b) (6). The subject was discharged on (b) (6) but was re-hospitalized on (b) (6) due to diarrhea and vomiting 8 days after IV pantoprazole dose. The subject also had otitis media during this time and was treated. The subject was discharged on (b) (6), after all symptoms were resolved. Vomiting and diarrhea were deemed as SAEs and unrelated to the study drug.
- Subject (b) (6) (18 months of age, male, Black; 1.6 mg/kg single IV pantoprazole dose; 13.6 mg): The subject had a history of stridor associated with laryngomalacia and pneumonia. The subject was admitted to the hospital on (b) (6), for a supraglottoplasty and received a single 1.6 mg/kg IV dose of pantoprazole (13.6 mg) after surgery. The subject was discharged on (b) (6). On (b) (6), the subject underwent observation for stridor and was released with a 5-day course of dexamethasone. The subject was readmitted on (b) (6), for worsening stridor and a chest X-ray consistent with pneumonia. The subject was treated with epinephrine and antibiotics and was discharged on (b) (6). The subject also had mild fever 5 days postdose. Worsening stridor was deemed as an SAE and unrelated to the study drug.
- No meaningful changes were noted in clinical laboratory values, vital signs, and electrocardiograms in this study in subjects 1 to 2 years of age.

Study 3001K1-110-US enrolled hospitalized pediatric subjects aged 2 to 16 years, inclusive, who could benefit from acid suppression therapy. After enrollment, all subjects were stratified by age into one of three groups: age 2 to 4 years, age 5 to 10 years, or age 11 to 16 years. All subjects were then randomly assigned to receive a single IV pantoprazole at a dose of 0.8 mg/kg or 1.6 mg/kg. The subjects were allowed to receive a single IV dose if the investigator deemed it as acceptable. The study enrolled 19 subjects (2 to 14 years of age; predominantly White [10/19] and male [11/19]) with approximately equal distribution across the three age subgroups; all were extensive metabolizers of CYP2C19. The subjects had significant past medical histories for cardiovascular disease (4), complications associated with closed head injuries (3), surgical procedures for idiopathic scoliosis (2), and radiation therapy for an anterior mediastinal mass.

Adverse events were evaluated up to 7 days post-dose, and 36.8% of the subjects had one or more TEAEs. There were no discontinuations due to AEs. A total of 14 AE terms, with 1 or more AEs per subject, were reported in 7 of the 19 subjects (36.8%) enrolled in the study. These terms (some reported terms are provided for clarity) included accidental injury, respiratory failure (respiratory failure secondary to closed head injury), dyspnea (respiratory distress), hypokalemia, hypoproteinemia (hypoalbuminemia), stridor, local reaction to procedure (postoperative complication), pancreas disorder (worsening of pancreatic pseudocyst), lung disorder (reintubation; mucus plug in airways), moniliasis (*Candida albicans* in endotracheal tube), pneumonia (nosocomial), fever, and pharyngitis. Of these reported AEs, three mild events of pharyngitis, fever, and hematemesis were deemed as TEAEs (per the protocol criteria) and

occurred in subjects 11 to 16 years old. Reported AEs included three non-treatment emergent, serious events:

- Subject [redacted] (14 y/o, female; 0.8 mg/kg; two doses of 71.6 mg q12h): The subject was hospitalized for recurring pancreatitis; IV dosing was on [redacted]. On [redacted] the subject experienced abdominal pain; magnetic resonance imaging showed worsening of pancreatic pseudocyst (day 5), and the subject underwent surgery. The subject also had an infection and local reaction related to the surgical procedure on day 20.
- Subject [redacted] (7 y/o, male; 1.6 mg/kg; two doses of 40 mg q12h): The subject was admitted to the hospital for a closed head injury secondary to a fall. Intravenous dosing was on [redacted] (two 40-mg doses). The subject had neurological deterioration and respiratory failure (secondary to closed head injury) 5 days after dosing.
- Subject [redacted] (9 y/o, male, 1.6 mg/kg; 59.2 mg; single dose): The subject was hospitalized for pulmonary edema and respiratory failure requiring mechanical ventilation; IV dosing was on [redacted]; on day 5, the subject experienced dyspnea; the subject had hypertension, poor vascular perfusion, and increased agitation, and was reintubated.

Single IV doses of pantoprazole (0.8 mg/kg, or 1.6 mg/kg) were evaluated in pediatric subjects 1 to 2 years and 2 to 16 years of age in the legacy IV studies. Adverse events, some serious, were confounded by complicated medical history of the pediatric subjects. Causality is difficult to discern from this single-arm, open-label study in the absence of a randomized concurrent comparator.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Not applicable.

23. Labeling: Key Changes

This prescribing information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the currently approved PI and the Applicant's draft PI (Table 32). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 32. Key Labeling Changes and Considerations[1]

Full PI Sections[2]	Rationale for Major Changes to Finalized PI[3] Compared to the Currently Approved PI and Applicant's Draft PI
INDICATIONS AND USAGE	The information for this indication was revised to describe the disease being treated and the appropriate patient population, and expand the indication for GERD with a history of EE to include pediatric patients 3 months and older. The revised wording is: "PROTONIX I.V. is indicated for treatment of: • Gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE) for up to 10 days in adults and up to 7 days in pediatric patients 3 months and older. • Pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome in adults. Limitations of Use The safety and effectiveness of PROTONIX I.V. for the treatment of upper gastrointestinal bleeding have not been established in adult or pediatric patients."

Continued

Table 32, continued

Full PI Sections[2]	Rationale for Major Changes to Finalized PI[3] Compared to the Currently Approved PI and Applicant's Draft PI
INDICATIONS AND USAGE (continued)	The following statements were removed from the approved adult indication and proposed [(b) (4)], because there are no reasonable concerns about safety or efficacy with durations of use longer than included in the respective indication(s): • Safety and efficacy of PROTONIX I.V. as a treatment of patients with GERD and a history of EE for more than 10 days have not been demonstrated. [(b) (4)] To describe the recommended duration of use, [(b) (4)] adult [(b) (4)] indications were revised to remove the descriptor of "short-term" and instead specify the recommended duration of treatment in number of days. The duration of the adult indication was revised from "7 to 10 days" to "up to 10 days" so as not to imply that a minimum of 7 days of treatment is needed. Based on the available data (See Sections 14.5 and 15.1), the duration of the pediatric indication is recommended to not exceed 7 days. The age group for the pediatric indication was revised [(b) (4)] to 3 months and older. As described in this document, in pediatric subjects 1 to <11 months of age, the characterization of the pharmacokinetics of intravenous pantoprazole relied on pharmacokinetic data obtained with oral pantoprazole. Assumptions of bioavailability could not be reliably characterized in pediatric subjects less than 3 months of age. See Section 6.3.1. Finally, information found in the DOSAGE AND ADMINISTRATION section was used to create a new Limitations of Use (LOU) statement concerning unapproved use for treatment of upper gastrointestinal bleeding: Limitations of Use The safety and effectiveness of PROTONIX I.V. for the treatment of upper gastrointestinal bleeding have not been established in adult or pediatric patients. For additional discussion on the LOU see below.

Continued

Table 32, continued

Full PI Sections[2]	Rationale for Major Changes to Finalized PI[3] Compared to the Currently Approved PI and Applicant's Draft PI
DOSAGE AND ADMINISTRATION	GERD and a History of EE For pediatric patients, the Applicant's table containing the recommended pediatric dosage regimen by age and body weight was revised to include the body weight cut-off for subjects 3 months to less than 1 year of age (<12.5 kg and 12.5 kg and above). The minimum body weight for pediatric patients 1 year to 17 years of age was revised from (b) (4) to "up to 15 kg." (b) (4) Safety of Protonix IV beyond 10 days in adults and 7 days in pediatric patients has not been evaluated, and prolonged use is not recommended. A (b) (4) proposed by the Applicant was removed and replaced with statements to switch to oral therapy as soon as feasible: For adults: "Discontinue PROTONIX I.V. as soon as the patient is able to tolerate oral treatment. Switch to an appropriate oral medication within 10 days of starting PROTONIX I.V." For pediatric patients 3 months of age and older: "Discontinue PROTONIX I.V. as soon as the patient is able to tolerate oral treatment. Switch to an appropriate oral medication within 7 days of starting PROTONIX I.V." Although there is no commercially available dosage formulation of oral Protonix appropriate for patients <5 years of age, given that there are other PPIs with oral dosage formulation approved down to 1 month of age (see Table 5), same statement to switch to oral therapy as soon as feasible in pediatric patients is recommended. Under adult patient dosage section, the Applicant had previously included the following statement with a prior CBE-0 supplement dated May 4, 2001. "Data on the safe and effective dosing for conditions other than those described *[see Indications and Usage (1)]* such as life-threatening upper gastrointestinal bleeds, are not available. PROTONIX I.V. 40 mg once daily does not raise gastric pH to levels sufficient to contribute to the treatment of such life-threatening conditions." *Continued*

Table 32, continued

Full PI Sections[2]	Rationale for Major Changes to Finalized PI[3] Compared to the Currently Approved PI and Applicant's Draft PI
DOSAGE AND ADMINISTRATION (continued)	Based on literature data, PPI dosages higher than 40 mg once daily have been used to prevent rebleeding following therapeutic endoscopy (i.e., as continuous infusion or loading dose followed by multiple daily bolus doses). The significance of a pH >6 in achieving and maintaining clotting is primarily theoretical and pH monitoring is not used clinically to adjust the PPI dose in this scenario.[27] Because there is reasonable concern about the safe and effective dosage of Protonix I.V. in the setting of upper gastrointestinal bleeding for both adult and pediatric patients, this information is more appropriate moved to the INDICATIONS AND USAGE section and reworded as a LOU, as shown above. <u>Pathological Hypersecretion including Zollinger-Ellison Syndrome</u> The recommended dosage for the indication of pathological hypersecretion including Zollinger-Ellison Syndrome was revised to remove the following statements which describe the clinical studies that supported approval of this indication and do not reflect the maximum dose or duration of treatment: "Daily doses higher than 240 mg or administered for more than 6 days have not been studied *[see Clinical Studies (14)]*." The following statements were revised to clarify the intent and to remove discussion of theoretical clinical complications "Transition from oral to intravenous and from intravenous to oral formulations of gastric acid inhibitors should be performed in such a manner to ensure continuity of effect of suppression of acid secretion. Patients with ZE Syndrome may be vulnerable to serious clinical complications of increased acid production even after a short period of loss of effective inhibition." The revised statement is: "When switching between intravenous to oral formulations of gastric acid inhibitors, consider the pharmacodynamic action of the drugs to ensure continuity of acid suppression."

Continued

[27] L Laine, A Barkun, J Saltzman, M Martel, G Leontiadis, 2021, ACG Clinical Guideline: Upper Gastrointestinal and Ulcer Bleeding, Am J Gastroenterol, 116(5):899-917

Table 32, continued

Full PI Sections[2]	Rationale for Major Changes to Finalized PI[3] Compared to the Currently Approved PI and Applicant's Draft PI
WARNINGS AND PRECAUTIONS	*Injection Site Reactions* The following statement was added: "Thrombophlebitis was associated with the administration of PROTONIX I.V. Assess the patient and remove the catheter if clinically indicated."
ADVERSE REACTIONS, *Clinical Trials Experience*	A description of the safety in Study B1791089 (see Section 7.6.1) was added to include a comparison of IV and oral safety in adults and pediatrics: "Adverse reactions reported with single and multiple doses of PROTONIX I.V. in 18 hospitalized pediatric patients 1 to 16 years of age were generally similar to those reported in adults with intravenous or oral pantoprazole sodium and in pediatric patients treated with oral pantoprazole sodium in clinical trials. Additionally, upper respiratory tract infection and otitis media were reported in pediatric patients treated with oral pantoprazole sodium."
USE IN SPECIFIC POPULATIONS	*Section 8.4 Pediatric Use* The data that supported the pediatric approval of the indication of GERD and a history of EE for up to 7 days in pediatric patients 3 months and older was revised to the data considered in the review (See Section 6). The Applicant's reference to (b) (4) was removed. The revised statement(s) are: "Use of PROTONIX I.V. for this indication is supported by evidence from adequate and well-controlled studies of intravenous and oral pantoprazole sodium in adults and oral pantoprazole in pediatric patients, with additional pharmacokinetic and safety data of intravenous pantoprazole in pediatric patients aged 1 year and older and oral pantoprazole in pediatric patients aged 3 months and older. Adverse reactions were generally similar to those reported in adults with intravenous or oral pantoprazole sodium *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3)]*."

Continued

Table 32, continued

Full PI Sections[2]	Rationale for Major Changes to Finalized PI[3] Compared to the Currently Approved PI and Applicant's Draft PI
USE IN SPECIFIC POPULATIONS (continued)	(b) (4) [redacted] The pediatric indication for Protonix IV is limited to short duration of treatment up to 7 days, (b) (4) [redacted] Animal Toxicity Data The description of a pre- and postnatal rat toxicity study was removed under this subheading as it is already included in the *Pregnancy* subsection. *Geriatric Use* The following text was added to describe the results of a pharmacokinetic study in geriatric subjects, as required by the labeling regulations (21 CFR 201.57): "No clinically meaningful differences in the pharmacokinetics of pantoprazole were observed in geriatric subjects compared to younger adult subjects *[see Clinical Pharmacology (12.3)]*." *Continued*

Table 32, continued

Full PI Sections[2]	Rationale for Major Changes to Finalized PI[3] Compared to the Currently Approved PI and Applicant's Draft PI
CLINICAL PHARMACOLOGY	*Pharmacokinetics* Pediatric Patients (b) (4) was removed and refocused on the information included in the model: "The pharmacokinetics of pantoprazole were studied in 40 pediatric patients 1 to less than 16 years of age in three open-label clinical trials in pediatric patients with GERD following intravenous administration and 180 pediatric patients from birth to 16 years of age in four randomized, open-label clinical studies in pediatric patients with GERD following oral administration." A limitation of the population pharmacokinetic analysis was added, to support the labeling recommendations in the pediatric age group of 3 months of age and older: "The pharmacokinetics of pantoprazole following intravenous administration in pediatric patients less than 3 months of age have not been characterized."

Source: Reviewer generated based on PI submitted October 31, 2023 in Module 1.14 of the sNDA
[1] Some sections may not be included because those sections may not have major issues (or changes).
[2] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[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

23.1. Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA-approved:

- PI

24. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended with this approval.

25. Financial Disclosure

Table 33. Covered Clinical Study: B1791089: An Open-Label, Multicenter Study To Evaluate the Pharmacokinetics of Single and Multiple Intravenous Doses of Pantoprazole in Two Age Cohorts of Hospitalized Pediatric Subjects 1 to 16 Years of Age Who Are Candidates for Acid Suppression Therapy

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 33		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not Applicable Significant payments of other sorts: Not Applicable Proprietary interest in the product tested held by investigator: Not Applicable Significant equity interest held by investigator: Not Applicable Sponsor of covered study: Not Applicable		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation(s): FDA, Food and Drug Administration

26. References

Please see footnotes.

27. Review Team

Table 34. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Andrew Chi
Nonclinical reviewer	Achinto Saha
Nonclinical team leader	Sushanta Chakder
OCP reviewer(s)	Tao Liu
OCP team leader(s)	Shen (Steven) Li, Jiang Liu
Clinical reviewer	Sandhya Apparaju
Clinical team leader	Suna Seo
Cross-discipline team leader	Suna Seo
Associate Director of Labeling	Joette Meyer
Division deputy director (clinical) (designated signatory authority	Juli Tomaino

Abbreviation(s): OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 35. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Kaining Zhi, Ramesh Gopalaswamy
OSE/DEPI	Joel Weissfeld, Benjamin Booth
OSE/DMEPA	Sherly Abraham, Damon Birkenmeier
DPMH	Amy Taylor, Shetarra Walker
CDS	Salman Hosain, Ling Cao
Medical Editors	Hyo Sook Song, Allison Cruz
Other	

Abbreviation(s): DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-36 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Kaining Zhi OPQAII DPQAXI	Sections: 9. Product Quality	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Kaining Zhi			**Digitally signed by Kaining Zhi** **Date: 8/12/2024 2:42 PM EDT** **GUID: 2024812184233**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Shen Li OCP DIIP	Sections: 5.2, 6.1, 6.3, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Shen Li			**Digitally signed by Shen Li** **Date: 8/12/2024 2:49 PM EDT** **GUID: 2024812184945**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Joette Meyer OII DG	Sections: 23 - 26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Joette Meyer			**Digitally signed by Joette Meyer** **Date: 8/12/2024 2:49 PM EDT** **GUID: 2024812184953**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Joette Meyer OII DG	Sections: 23 - 26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Joette Meyer			**Digitally signed by Joette Meyer** **Date: 8/12/2024 2:50 PM EDT** **GUID: 2024812185024**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Ramesh Gopalaswamy OPQAII DPQAXI	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Ramesh Gopalaswamy			**Digitally signed by Ramesh Gopalaswamy** **Date: 8/12/2024 2:51 PM EDT** **GUID: 2024812185129**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Sandhya Apparaju OII DG	Sections: All	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sandhya Apparaju			**Digitally signed by Sandhya Apparaju** **Date: 8/12/2024 3:12 PM EDT** **GUID: 2024812191220**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Suna Seo OII DG	Sections: All	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Suna Seo			**Digitally signed by Suna Seo** **Date: 8/12/2024 3:14 PM EDT** **GUID: 2024812191456**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Tao Liu OCP DIIP	Sections: 5.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Tao Liu			**Digitally signed by Tao Liu** **Date: 8/12/2024 3:35 PM EDT** **GUID: 2024812193553**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Achinto Saha OII DPTII	Sections: 5, 7, 8, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	The NDA is approvable from nonclinical standpoint.

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Achinto Saha			**Digitally signed by Achinto Saha** **Date: 8/12/2024 3:59 PM EDT** **GUID: 2024812195934**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Sushanta Chakder OII DPTII	Sections: 5, 7, 8, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sushanta Chakder			**Digitally signed by Sushanta Chakder** **Date: 8/12/2024 4:02 PM EDT** **GUID: 202481220211**	

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/

SUNA C SEO
08/12/2024 04:22:02 PM

JULI A TOMAINO
08/12/2024 04:28:11 PM