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APPLICATION NUMBER:

209463Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209,463
Priority or Standard	Standard
Received Date(s)	June 7, 2016
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Division / Office	DGIEP/ODE 3
Reviewer Name	Marjorie F. Dannis, M.D.
Review Completion Date	May 15, 2017
Established Name	Pantoprazole Sodium
(Proposed) Trade Name	Pantoprazole Sodium
Therapeutic Class	Proton Pump Inhibitor (PPI)
Applicant	Exela Pharma Sciences
Formulation(s)	Solution for Intravenous Injection
Dosing Regimen	Gastroesophageal reflux disease (GERD) associated with erosive esophagitis (EE): 40 mg IV daily for 7-10 days Pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome: 80 mg IV every 12 hours
Indication(s)	Short-term treatment (7-10 days) of patients with GERD and a history of EE *and* Treatment of pathological hypersecretory conditions (ZE Syndrome)
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the current submission, the Sponsor (Exela Pharma Sciences) is proposing the following indications for pantoprazole sodium injection (NDA 209,463) in adults:

- Short-term treatment (7-10 days) of patients with GERD and a history of erosive esophagitis (EE)
- Treatment of pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome

From a clinical standpoint, this reviewer recommends the approval of pantoprazole sodium injection (NDA 209,463) for the proposed indications if no other discipline has deficiencies that preclude approval.

1.2 Risk Benefit Assessment

The active ingredient in pantoprazole sodium injection has been available in the US market since 2001 as Protonix IV. During this time, various safety labeling changes have been made to the product label[1]. However, most of these labeling changes were class labeling changes and were applicable to long-term PPI use. The drug contains no boxed warnings. The Sponsor submitted a 505(b)(2) application relying on the Agency's finding of safety and efficacy of Protonix IV.

The proposed new formulation provides the equivalent amount of active ingredient as Protonix IV, the reference listed drug. Exela's pantoprazole sodium differs from the reference listed drug (RLD) with respect to one inactive ingredient. The RLD product contains Edetate Disodium (a chelating agent (b) (4) whereas Exela's formulation does not. **Thus, the only difference between Exela's pantoprazole sodium for Injection and the RLD is the removal of Edetate Disodium (EDTA).**

The reference drug, Protonix IV, is known to be efficacious (for the short-term treatment of patients with GERD and history of EE *and* treatment of pathological hypersecretory conditions including ZE Syndrome) and relatively safe. As long as Exela's pantoprazole sodium injection can be safely administered (b) (4) then the known benefits of the product outweigh the known risks.

1 This includes oral formulations of active ingredient.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

N/A

1.4 Recommendations for Post-market Requirements and Commitments

No post-market requirements and/or commitments are recommended. Pantoprazole sodium does not contain a new active ingredient, new indication(s), new dosage form(s), new dosing regimen(s), or new route(s) of administration compared to Protonix IV, the reference drug. Therefore, as per the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the Sponsor is not required to evaluate the use of pantoprazole sodium injection in the pediatric population for the same indications as adults.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed drug product, pantoprazole sodium for injection, 40 mg/vial, (a parenteral preparation supplied as 40 mg/ 10 mL single-dose vial) is a PPI. Under Section 505(b)(2), Protonix (pantoprazole sodium) for Injection, is identified as the previously approved drug approved on March 22, 2001, by the Sponsor and NDA holder, Wyeth Pharmaceuticals, Inc., for which FDA has made a finding of safety and effectiveness. The formulation for Exela's pantoprazole sodium for injection has the same active ingredient, dosage form, route of administration, and indications as the reference listed drug Wyeth Pharmaceutical's Protonix IV.

Exela's pantoprazole sodium for injection differs from the reference listed drug with respect to the inactive ingredients that are present in the RLD. The RLD product contains 1 mg/vial Edetate Disodium (chelating agent / (b) (4)) and Sodium Hydroxide (pH adjuster); whereas Exela's formulation contains only Sodium Hydroxide as a pH adjuster. (b) (4) **Thus, the only difference between Exela's pantoprazole sodium for injection and the RLD is the removal of EDTA.**

2.2 Currently Available Treatments for Proposed Indications

These are several other PPIs which are approved for the proposed indications[2].These include:

- Lansoprazole
- Omeprazole
- Esomeprazole
- Rabeprazole
- Dexlansoprazole
- Omeprazole/sodium bicarbonate

In addition, several histamine-2 receptor antagonists (H_2RA), ranitidine, famotidine, and cimetidine are approved for both of the proposed indications whereas nizatidine is approved for treatment of patients with GERD and EE.

2.3 Availability of Proposed Active Ingredient in the United States

Pantoprazole sodium Injection, as Protonix IV, was originally approved by the FDA on March 22, 2001. It is currently available as Protonix IV and also available as multiple generics.

In this NDA application, the Sponsor submits pantoprazole sodium Injection as an alternative formulation to the referenced Protonix IV product.

2.4 Important Safety Issues With Consideration to Related Drugs

The labeling of all PPIs contains various warnings and precautions, which over the last several years have increased in number. Below is the **WARNINGS AND PRECAUTIONS HIGHLIGHTS** section of the most recent Protonix IV label which was last updated on October 24, 2016.

- *In adults, symptomatic response to therapy with PROTONIX I.V. does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing*
- *Anaphylaxis has been reported with use of intravenous pantoprazole*
- *Thrombophlebitis is associated with the administration of intravenous pantoprazole*
- *Zinc supplementation should be considered in patients treated with PROTONIX I.V. for Injection who are prone to zinc deficiency. Caution should be used when other EDTA containing products are also co-administered intravenously*

2 or indications with similar wording as not all PPIs have the consistently worded indications.

- *Acute interstitial nephritis has been observed in patients taking PPIs.*
- *PPI therapy may be associated with increased risk of Clostridium difficile-associated diarrhea*
- *Bone Fracture: PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine after long term and multiple daily dose*
- *Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue PROTONIX I.V. and refer to specialist for evaluation*
- *Elevations of transaminases observed in clinical studies*
- *Hypomagnesemia has been reported rarely with prolonged treatment with PPIs*

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Protonix (pantoprazole sodium) Injection (NDA 20-988) was originally approved by the FDA on March 22, 2001 for the short-term treatment (7 to 10 days) of patients having gastroesophageal reflux disease with a history of erosive esophagitis as an alternative to oral therapy in patients who are unable to continue taking Protonix (pantoprazole sodium) Delayed-Release Tablets. On October 19, 2001, the FDA approved NDA 20-988/S003, which provided for the use of Protonix IV for Injection in the treatment of pathological hypersecretion associated with Zollinger-Ellison Syndrome.
The admixture compatibility studies submitted to the original NDA for Protonix IV demonstrated a (b) (4) precipitate that formed upon reconstitution of the lyophilized powder of pantoprazole and when the reconstituted solution was diluted in 100 mL (b) (4) solutions prior to administration**. Based upon the formation of the precipitate, the approved labeling for Protonix IV required that the product be administrated intravenously** (b) (4) **.**
In addition, the approval letter, dated March 22, 2001, provided the following postmarketing commitment:

"To provide a proposal to eliminate the filtration requirement for the product. The time frame for this commitment is 2 years after NDA approval date."

(b) (4)

In the current application, Exela Pharma Sciences requests approval of their proposed drug product, pantoprazole sodium for Injection, 40 mg/vial, a parenteral preparation supplied as 40 mg/vial in a 10 mL single-dose vial. In accordance with 314.54(a)(1)(iii) and under Section 505(b)(2), Protonix (pantoprazole sodium) for Injection, was

identified as the previously approved drug under NDA No. 20988, approved on March 22, 2001, by the Sponsor and NDA holder, Wyeth Pharmaceuticals, Inc., for which FDA has made a finding of safety and effectiveness.

The formulation for Exela's pantoprazole sodium for Injection has the same active ingredient, dosage form, route of administration, and indications as the reference listed drug Wyeth Pharmaceutical's Protonix (pantoprazole sodium) for injection and the only difference between Exela's pantoprazole sodium for Injection and the RLD is the removal of Edetate Disodium.

2.6 Other Relevant Background Information

Relevant background information is discussed in other sections of this review. Of note is that with removal of EDTA from this formulation, the previous concerns regarding Zinc deficiency (secondary to EDTA) as described in the current labeling of Protonix IV, are no longer relevant. (b) (4)

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The application was electronic, non-ECTD format and the overall quality was acceptable.

3.2 Compliance with Good Clinical Practices

No clinical trials were conducted for this 505(b)(2) application.

3.3 Financial Disclosures

No clinical trials were conducted for this 505(b)(2) application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Manufacturing and Controls (CMC) drug product review of the current submission was not completed at the time of this clinical review. According to the Drug Substance Reviewer, Sukhamaya (Sam) Bain, Ph.D. “From the API perspective, the NDA is recommended for approval”.
However, outstanding CMC issues include whether the product without EDTA (b) (4) .

4.2 Clinical Microbiology

No new micro studies were submitted for review.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical/toxicology studies were submitted for review.

4.4 Clinical Pharmacology

No new clinical pharmacology studies were submitted for review.

4.4.1 Mechanism of Action

As per the Protonix IV label

4.4.2 Pharmacodynamics

As per the Protonix IV label

4.4.3 Pharmacokinetics

As per the Protonix IV label

5 Sources of Clinical Data

No clinical trials were submitted to support the efficacy of the proposed product.

6 Review of Efficacy

Efficacy Summary

The proposed product is relying upon the Agency's findings of safety and efficacy of Protonix IV.

6.1 Indication

Pantoprazole Sodium for Injection is indicated for:

- Short-term treatment (7-10 days) of patients with GERD and a history of EE *and*
- Treatment of pathological hypersecretory conditions including ZE Syndrome

6.1.1 Methods

N/A

6.1.2 Demographics

N/A

6.1.3 Subject Disposition

N/A

6.1.4 Analysis of Primary Endpoint(s)

N/A

6.1.5 Analysis of Secondary Endpoints(s)

N/A

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

N/A

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

N/A

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

N/A

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

No new safety data was submitted using the proposed drug product.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

N/A

7.1.2 Categorization of Adverse Events

N/A

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.2 Explorations for Dose Response

N/A

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

N/A

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

N/A

7.3 Major Safety Results

N/A

7.3.1 Deaths

N/A

7.3.2 Nonfatal Serious Adverse Events

N/A

7.3.3 Dropouts and/or Discontinuations

N/A

7.3.4 Significant Adverse Events

N/A

7.3.5 Submission Specific Primary Safety Concerns

In the current application, Exela Pharma Sciences requests approval of their proposed drug product, pantoprazole sodium for injection, which has the same active ingredient, dosage form, route of administration, and indications as the RLD, Wyeth Pharmaceutical's Protonix IV. The only difference between Exela's pantoprazole sodium for injection and the RLD is the removal of EDTA.

(b) (4)

Thus, with the removal of EDTA, CMC data must confirm that Exela's pantoprazole sodium IV can be safely administered (b) (4). At the current time, the final analysis of the CMC data is not available, but preliminary review appears to show that Exela's pantoprazole sodium IV can be safely administered (b) (4).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

N/A

7.4.2 Laboratory Findings

N/A

7.4.3 Vital Signs

N/A

7.4.4 Electrocardiograms (ECGs)

N/A

7.4.5 Special Safety Studies/Clinical Trials

N/A

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

N/A

7.5.3 Drug-Demographic Interactions

N/A

7.5.4 Drug-Disease Interactions

N/A

7.5.5 Drug-Drug Interactions

N/A

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

N/A

7.6.2 Human Reproduction and Pregnancy Data

N/A

7.6.3 Pediatrics and Assessment of Effects on Growth

The Sponsor is not proposing a new active ingredient, a new dosage form, a new dosing regimen, or a new route of administration. Therefore, as per Section 505(a)(1) of the Food, Drug and Cosmetic Act, the Sponsor acknowledges that the Pediatric Research Equity Act (PREA) does not apply to this application and therefore the Applicant has requested a full waiver of pediatric studies.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

N/A

8 Postmarket Experience

Exela's pantoprazole sodium injection is not a currently marketed product thus there is no postmartketing experience available for this product.

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/s/

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05/16/2017

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05/16/2017