

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209463Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 20, 2017
From	Hitesh Shroff, Ph.D., CMC lead (Acting) CDER/ONDP II/Branch V
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 209463
Applicant	Exela Pharma Sciences, LLC, Lenoir, NC, USA
Date of Submission	June 6, 2016
PDUFA Goal Date	July 7, 2017
Proprietary Name / Established (USAN) names	Pantoprazole Sodium for Injection (pantoprazole sodium)
Dosage forms / Strength	40 mg pantoprazole lyophilized powder in single-dose vial for reconstitution
Proposed Indication(s)	<u>Adults:</u> <ul style="list-style-type: none"> • Short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD) associated with a history of erosive esophagitis (EE) • Pathological hypersecretion conditions, including Zollinger-Ellison (ZE) syndrome
Recommended:	Approval

1. Introduction

Pantoprazole sodium for injection is a proton pump inhibitor. It is supplied in a single-dose vial as sterile lyophilized powder containing 40 mg of pantoprazole equivalent to 45.1 mg of pantoprazole sodium. The drug product is reconstituted with 10 mL 0.9% Sodium Chloride Injection or Lactated Ringer's solution and administered as intravenous infusion. It will be manufactured by Exela Pharma Sciences, LLC.

The NDA has been filed as a 505(b)(2) application, using Protonix IV (pantoprazole sodium) for injection, 40 mg, distributed by Wyeth Pharmaceuticals, Inc., PA as the RLD. Protonix IV was approved in 2004 under NDA 020988 for the same indications. The applicant relied on the efficacy and safety findings of Protonix IV. There is no IND associated with this NDA and no clinical data was submitted for approval of this NDA.

The proposed drug product has the same route of administration, dosage form, dosing regimen, active ingredient, strength and indications as the RLD. **The only difference is that Protonix IV contains 1 mg/vial EDTA but the proposed drug product does not contain EDTA in its formulation.** The lack of EDTA in the drug product formulation is not expected to affect its in vivo PK performance, efficacy and safety of the drug product. Both drug products contain sodium hydroxide to adjust pH but there no other excipients, antioxidants or preservatives.

Due to the similarities between Exela's proposed drug product and RLD in terms of active ingredient, pH, viscosity, osmolality and applicant's biowaiver request for the in vivo BA/BE studies with justification submitted under 21 CFR 320.24(b)(6) a biowaiver for in vivo BA/BE studies was granted.

2. Background

Pantoprazole sodium for injection is a proton pump inhibitor (PPI). It is indicated for short term gastroesophageal reflux disease (GERD) as well as Pathological hypersecretion conditions including Zollinger-Ellison (ZE) syndrome. The recommended dosage for patients with GERD associated with EF the recommended adult dosage is 40 mg administered once daily by IV infusion for 7 to 10 days. For pathological hypersecretory conditions including ZE syndrome the recommended adult dosage is 80mg administered every 12 hours by IV infusion. The IV infusion can be administered over 2 minutes or 15 minutes.

Protonix IV (pantoprazole sodium) for injection, 40 mg from Wyeth Pharmaceuticals was approved in January 2001 (NDA 020988). However, due to precipitates in reconstituted

(b) (4)

The proposed drug product formulation (b) (4) RLD except that it does not contain EDTA. Exela also claimed that there is no significant precipitates formation during reconstitution of the drug product. Exela compared precipitates formation in side by side comparison of both RLD and drug product in different IV diluents and different pH. The results confirmed that there was less precipitation in the drug product solution than RLD (b) (4). Thus, with respect to overall quality, the drug product from Exela appears to be comparable to RLD.

3. CMC/Device

Drug substance: The active pharmaceutical ingredient in the proposed drug product is pantoprazole sodium, USP. It is a white to almost white powder. It is a BCS Class III compound with high water solubility and low permeability. The quality of the API is controlled by its specification which includes identification by IR and UV spectroscopy; purity by HPLC, heavy metals per USP <231> and impurities by HPLC etc. The CMC information for the drug substance was provided in DMF (b) (4). The DMF was reviewed by Dr. Sam Bain and determined to be adequate. Thus from drug substance from quality perspective this NDA is recommended for approval.

Drug Product: The proposed drug product pantoprazole sodium for injection is supplied in single-dose 10 mL clear glass vials as a white to off-white sterile lyophilized powder for reconstitution. Each vial contains 40 mg of pantoprazole (equivalent to 45.1 mg of

pantoprazole sodium). The vials are stoppered with rubber stoppers and capped with white flip-off overseals.

The proposed drug product formulation

(b) (4)

Its manufacturing process involves typical

(b) (4)

(b) (4)

(b) (4) The drug product manufacturing process was reviewed and determined to be acceptable by Dr. Yuesheng Ye. This NDA was recommended for approval from the drug product manufacturing process perspective.

The microbiology reviewer, Dr. Julie Nemecek, evaluated sterilization, sterile filtration process, container closure integrity, manufacturing process for sterile product, environmental monitoring program for (b) (4) processing and testing, and verification of endotoxins tests. All of the provided information was judged to be adequate and approval of this NDA was recommended from the microbiology perspective.

The drug product specification included the critical product quality attributes for identity, strength, purity and quality including appearance, identity, assay, impurities, pH, content uniformity of dosage units, sterility, endotoxins and particulate matter. In addition specification also included reconstitution solution description, clarity, container closure appearance and visual particulate matter tests. Based on the satisfactory stability data 24-month of expiration dating period is granted when drug product is stored at room in the proposed container closure system. The drug product specification and stability data were evaluated by Dr. Caroline Strasinger and determined to be adequate. This NDA was recommended for approval for drug product quality perspective.

The Office of Process and Facilities has made an “Adequate” recommendation for the drug substance and drug product manufacturing and testing facilities.

4. Nonclinical Pharmacology/Toxicology

Dr. Dinesh Gautam, the nonclinical pharmacology/toxicology reviewer, identified no nonclinical safety issues for the approval of the proposed drug product, Pantoprazole sodium for injection.

In this NDA Exela did not submit any nonclinical studies. The applicant relied on the Agency’s previous safety assessment of the RLD, Protonix IV. The drug product formulation contains only sodium hydroxide as a pH adjuster and EDTA is omitted. There were no safety issues identified with regard to the impurities or degradants in the drug product.

Since the sponsor did not submit any new nonclinical studies for this application the nonclinical sections of the labeling are adopted from the RLD labeling. For the proposed labeling changes see his review.

5. Clinical Pharmacology/Biopharmaceutics

Exela did not conduct any new clinical study and clinical pharmacology study. The applicant requested a biowaiver of BA/BE requirement per 21 CFR 320.22(a) for this drug product. The clinical pharmacology information in the proposed label is the same as in the labeling for the RLD, Protonix IV. The clinical pharmacology reviewer, Dr. Dilara Jappar, has recommended this NDA for approval from clinical pharmacology perspective.

Dr. Hansong Cheng, the OPQ Biopharmaceutics reviewer, granted a waiver of in vivo bioequivalence studies on the basis that the proposed drug product (b) (4) the RLD in terms of active ingredient, pH, viscosity and osmolality. It was concluded that the omission of EDTA (b) (4) expected to have no effect on the pharmacokinetics and clinical outcome of safety and efficacy of the drug product. The proposed drug product and the RLD are for IV use so their bioavailability is self-evident. From biopharmaceutics perspective this NDA was recommended for approval.

6. Clinical Microbiology

There are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical- Efficacy

The proposed drug, Pantoprazole sodium injection, is indicated for GERD and treatment of pathological hypersecretory conditions. The proposed drug product differs from the RLD, Protonix IV, with respect to one inactive ingredient, EDTA. The safety and efficacy of the proposed drug product is expected to be same as the RLD. The applicant did not conduct any clinical study instead relied on the Agency's previous finding of safety and efficacy for the RLD.

Dr. Marjorie F. Dannis the clinical reviewer recommended the approval of this NDA for the same indications and target populations as Protonix IV. A post-market risk evaluation and/or mitigation are not recommended.

8. Safety

The applicant did not submit any new safety data using the proposed drug product.

Protonix IV (pantoprazole sodium) for injection was initially approved by the FDA on March 22, 2001. It is also available as multiple generics. This drug product required a (b) (4) during intravenous administration of the drug product. In 2004 a new formulation of Protonix IV containing EDTA was approved. EDTA was added to

Protonix IV to (b) (4). This modified Protonix IV formulation can be administered (b) (4).

The only different between the proposed drug product and Protonix IV formulations is that the proposed drug product formulation does not contain EDTA. The applicant demonstrated that there is no significant precipitation during reconstitution. (b) (4)

The proposed drug product is a proton pump inhibitor (PPI) indicated for GERD. The labeling of all PPIs contains various warnings and precautions in the Warnings and Precautions section of the label.

9. Advisory Committee Meeting

No Applicable

10. Pediatrics

The proposed drug product does not contain a new active ingredient, a new dosage form, a new dosing regimen or a new route of administration. Therefore, in accordance with Section 505(a)(1) of the Food, Drug and Cosmetic Act the Pediatric Research Equity Act (PREA) does not apply to this application. The Pediatric Labeling reviewer from DPMH, Dr. Amy M. Taylor, concluded that the proposed drug product does not trigger PREA. Therefore there is no need to request a full waiver of pediatric studies under PREA.

11. Other Relevant Regulatory Issues

The following unexpired patents are listed in the Orange Book under NDA 020988 Protonix IV (pantoprazole sodium) for injection from Wyeth Pharmaceuticals Inc. Protonix IV is the reference listed drug (RLD) for the proposed drug product.

US Patent No. 6780881	- Expiry Date: Nov 17, 2021
US Patent No. 6780881*PED	- Expiry Date: May 17, 2022
US Patent No. 7351723	- Expiry Date: Nov 17, 2021
US Patent No. 7351723*PED	- Expiry Date: May 17, 2022
US Patent No. 8754108	- Expiry Date: Nov 17, 2021
US Patent No. 8754108*PED	- Expiry Date: May 17, 2022

Exela provided a Statement Concerning Notice to Patent Owner and NDA Holder stating that Exela will give notice as required by Section 505(b)(3) of the FDCA and 21 CFR 314.52(a) to each patent owner and to the holder of the new drug application. Exela will also amend its new drug application concurrent with sending the notices, as required by 21 CFR 314.52(b).

12. Labeling

The proposed drug product PI and container carton labels were adapted from the Protonix IV labels.

Dr. Meeta Patel, from the Office of Prescription Drug Promotion reviewed the draft PI for the proposed drug product and has no comments and concurred with the proposed PI.

The proposed labels and labeling were reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) reviewer, Mr. Mathew Barlow, and made recommendation to clarify information and promote the safe and effective use of the product.

The CMC reviewer, Dr. Caroline Strasinger, also reviewed the proposed labels and labeling from CMC perspective and made recommendations.

The pharmacology/toxicology reviewer, Dr. Dinesh Gautam, has made recommendations in relevant sections of the proposed labels and labeling.

The applicant has made changes to the labels and labeling as recommended by all disciplines.

13. Recommendations/Risk Benefit Assessment

Protonix IV (pantoprazole sodium) for injection for GERD and pathological hypersecretion conditions has been marketed since 2001 for patients who could not take Protonix delayed release tablets. (b) (4)

(b) (4)

Exela's proposed drug product without EDTA (b) (4) Protonix IV in safety and efficacy. Exela has demonstrated that there is no significant precipitation observed during reconstitution of the drug product (b) (4).

There are no unresolved issues or deficiencies to be conveyed to the applicant. No PMRs, PMCs or pediatric studies are requested.

The overall recommendation from all disciplines involved in the review of this NDA is that this NDA should be approved.

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/s/

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06/21/2017