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RESEARCH**

APPLICATION NUMBER:

209463Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD, MPH Deputy Director for Safety Division of Gastroenterology and Inborn Errors Products ODE III, OND CDER, FDA
Subject	Signatory Summary Review
NDA #	209463
Applicant Name	Exela Pharma Sciences
Date of Submission	June 7, 2017
PDUFA Goal Date	April 7, 2017; goal date extended due to major amendment July 7, 2017
Established (USAN) Name	Pantoprazole Sodium for Injection
Dosage Forms / Strength	Injection, 40 mg vial (lyophilized powered)
Proposed Indication(s)	<ul style="list-style-type: none"> • Short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis. • Treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome. <i>Intended population (adults)</i>
Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers:
OND Action Package, including:	
Medical Officer Review	Marjorie Dannis
Statistical Review	NA
Pharmacology Toxicology Review	Dinesh Gautam
OPQ Review/OBP Review	Sam Bain, Caroline Strasinger, Yuesheng Ye, Julie, Nemecek, Carl Lee, Hansong Chen, Oumou Barry, Hitesh Shroff, Palu Perdue Jr
CDTL Review	Hitesh Shroff
OSE/DMEP	Matthew Barlow
OSE/DEPI	Joel Weissfeld
OPDP	Meeta Patel
DPMH	Amy Taylor

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEP=Division of Medication Error Prevention
 DPMH = Division of Pediatric and Maternal Health
 DEPI: Division of Epidemiology
 CDTL=Cross-Discipline Team Leader
 OPDP= Office of Prescription Drug Promotion

1. Introduction

This 505(b)(2) new drug application, NDA 209463, Pantoprazole Sodium for Injection, was submitted by Exela Pharmaceutical Sciences on June 7, 2016. It relies on NDA 20988, Protonix I.V. (pantoprazole sodium) for injection, for intravenous use, as the Listed Drug (LD). It provides the equivalent amount of the active ingredient, pantoprazole, as the LD. The proposed drug differs from the reference product with respect to the inactive ingredients. Specifically, the LD contains Edetate Disodium (b)(4) and sodium hydroxide (pH adjuster), while the proposed product only contains the sodium hydroxide. However, the products share the same strength and dose, and are both available as a 40 mg per vial lyophilized powder. Thus, the only difference between Exela's pantoprazole sodium for injection and the LD is the absence of Edetate Disodium (EDTA).

Pantoprazole sodium is a proton pump inhibitory (PPI). It is indicated for

- Short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis.
- Treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome (intended population: adults).

Exela is requesting the same indications as approved in the LD professional labeling.

2. Background

The LD, Protonix IV (NDA 20988), was initially approved on March 22, 2001. During the development and subsequent approval of NDA 20988, the issue of precipitates forming in the product was observed. The original approval required this product to be packaged with an (b)(4). After additional development of this product, an NDA supplement was approved that no longer requiring (b)(4).

In this review it will be important to establish that the proposed drug product from Exela will not have a similar problem with particulates. The Applicant submitted data from side to side comparisons of the particulates in the LD and the new product in the presence of various intravenous diluents and at different pH conditions. (See section 3 for further discussion).

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

For complete regulatory history of this application see Medical Officer review (Marjorie Dannis).

3. OPQ/ CMC/ Biopharmaceutics

Overall Conclusion:

- The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

- The Office of Process and Facilities (OPF) has made a final overall “Approval” recommendation for the facilities involved in this application as of this review.
- The claim for the Categorical Exclusion for the Environmental Assessment is granted
- Addendum (June 13, 2017) final recommendation for approval, labeling issues resolved.

Drug Product Review:

In the summary review regarding the product, Dr. Moo-Jhong, Rhee commented on Dr. Strasinger’s review as follows: “I agree with Dr. Strasinger’s assessment on the overall quality control strategy presented in this application to assure the identity, strength, purity, and quality of the drug product, and therefore, I concur with her approval recommendation of this application from the drug product perspective.”

“One salient question raised by Dr. Caroline Strasinger during the review of this application was why this product (b) (4)

Additionally, she reviewed the effect of pH on the particles.

In her review she found that the submitted information did not provide any conclusive clue as to the nature of particulates. Dr. Rhee went on to comment “The elemental analysis of the drug product and RLD implicate (b) (4). Also interestingly, RLD has more particulates (b) (4). This may indicate that the chemistry behind the particulates maybe more complex than we thought. No matter what the nature of the particulates is, this new product has much less particulates than the RLD. (b) (4) would be at least as good as the RLD from the number of particulates point of view alleviating any significant safety concern to the patients.”

Biopharmaceutics Review:

“The Biopharmaceutics review focuses on the side-by-side comparison between the proposed product and the Listed Drug for the active and inactive ingredients including pH, viscosity, and osmolality, as well as the Applicant’s waiver request on the in vivo BA/BE for its proposed drug product.”

Side-by-Side Comparison of Physicochemical Characteristics between the Listed Drug and Proposed Formulation

Physicochemical Property	PROTONIX IV Lot #360315	Pantoprazole Sodium for Injection Lot #XLNF1431
Measured Reconstituted Product pH	9.83	9.96
pH Range for the Reconstituted Product	9.0-10.5 (labeled)	9.8-10.2 (based on 24 month stability data for 3 lots)

Osmolarity	310m Osm/kg	310m Osm/kg
Tonicity	Isotonic	Isotonic
Viscosity	0.016292 Centistokes	0.016292 Centistokes

These products have the same osmolarity, tonicity and viscosity. The reviewers found the pH of the two reconstituted solutions to be similar.

They concluded that: “Overall, no EDTA in the proposed drug product does not affect its in vivo PK performance and clinical outcome on efficacy/safety.”

“As consistent with 21 CFR 320.24(b)(6), the FDA deemed adequate information supporting the relative bioavailability of Exela’s proposed drug product to the Listed Drug and a scientific bridge has been established to the Agency’s finding of safety and effectiveness for the Listed Drug. Thus, additional in vivo bioequivalence (BE) bridging study is not needed. This Reviewer recommends that NDA 209463 for Pantoprazole Sodium for Injection, 40 mg/vial be approved from the Biopharmaceutics perspective.”

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance, and the biopharmaceutics assessment that the bridging study is not needed. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no other outstanding issues.

4. Nonclinical Pharmacology/Toxicology

For nonclinical safety, the Applicant relied on the Agency’s findings of the safety of the LD product. No new studies were conducted.

The nonclinical reviewers made recommendations to incorporate the new findings from a recently reviewed study of pre- and postnatal developmental toxicity in rats with additional endpoints to evaluate the effect on bone development with pantoprazole sodium into the labeling. This is further discussed under the pediatrics, and labeling sections below. It reflects new information that was recently added to the RLD labeling since the submission of this application.

The final approved labeling was reviewed and the nonclinical pharmacology/toxicology reviewers were in agreement with the findings reflected therein (see final approved label).

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

No new clinical pharmacology data were provided in this application. The clinical pharmacology reviewer was involved in labeling discussions and concurred with the final approved label (see final approved label).

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

This section does not apply to this application.

7. Clinical/Statistical-Efficacy

There were no clinical trials submitted in this application.

8. Safety

No clinical data was submitted in this application. The safety of the LD is unchanged.

9. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

In this application, Exela has requested a full waiver of pediatric studies. This application does not trigger PREA. Therefore, there is no need to request a full waiver of pediatric studies under PREA.

The safety and effectiveness of Pantoprazole Sodium for Injection in pediatric patients have not been established as reflected in the Protonix I.V.; NDA 20988, which is not approved for use in pediatric patients.

During our preliminary review of the submitted labeling, it was noted that Exela did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. We communicated this to the sponsor and stated that the proposed Pregnancy and Lactation Labeling Rule (PLLR) labeling changes cannot be agreed upon until the information request is fulfilled. The applicant submitted this data/literature to support this changes and it was reviewed during this review period.

Maternal Health Review

Exela proposed the addition of information regarding asthma and allergic disease in offspring of mothers exposed to PPI during pregnancy. This proposal was based upon data in two published articles. The Division of Epidemiology was consulted to review the literature and determine the strength of this evidence for labeling. DEPI reviewed the two articles submitted by Exela and six additional articles found in medical literature. These eight articles, reporting results from epidemiologic studies completed in six populations, contained information about associations between prenatal exposures to PPI or H2RA and childhood allergic disease, including asthma. The DEPI reviewers found that “The weight of evidence available from

these observational studies showed a higher frequency of allergy, including asthma, in children with prenatal exposure to PPI or H2RA. Bias due to confounding plausibly explains this association. The literature reviewed by DEPI contained very limited evidence for causal association between prenatal exposure to PPI or H2RA and childhood allergy.” This assessment was agreed upon by the maternal health reviewers as well as the DGIEP reviewers. This information was not included in Section 8.1 of the labeling. Other comments regarding wording of section 8.1 made by the maternal health reviewers were incorporated into the label.

Maternal and Pediatric Review

Results of the nonclinical pre- and post-natal study with a focus on bone toxicity have been incorporated into the LD labeling since the Maternal Health and Pediatric consult was written, and are also being incorporated into this 505(b)(2) label.

Pediatric and Maternal Health reviewers provided input into the labeling, Section 8, in Pregnancy and Lactation Labeling Rule (PLLR) format, and have found the final approved version acceptable. (See final approved label for details).

I agree with these findings and the final recommended and approved labeling.

11. Other Relevant Regulatory Issues

The 505(b)(2) committee has cleared this application for approval under these regulations. There are no other unresolved relevant regulatory issues.

12. Labeling

- **Product Naming:** Pantoprazole Sodium for Injection
- **Physician labeling:**
 - Addition of results of animal studies regarding bone and growth from the LD to Section 8 of the labeling.
 - Of note based upon the data reviewed and the PLLR format the following statement is listed in the Highlights of the label:
“USE IN SPECIFIC POPULATIONS-----
Pregnancy: Based on animal data, may cause fetal harm. (8.1)”
 - Additional minor adjustments were addressed by the applicant.
- **Carton and Container Labeling:** approved by OPQ and DMEP.
- **Patient labeling/Medication Guide:** This is an intravenous formulation and as such there is no Medication Guide (n. B, the oral PPIs do have a Medication Guide).

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** Approval
- **Risk Benefit Assessment:**

The benefit risk assessment of this product is unchanged in comparison to the approved listed drug product which is currently marketed as safe and effective. There were no new clinical safety issues identified during this review.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS):**
None required.
- **Recommendation for other Postmarketing Requirements and Commitments:**
None recommended, there were no new safety issues identified during this review which require safety studies.

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/s/

JOYCE A KORVICK
06/30/2017