

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209463Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 209463	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Pantoprazole sodium for injection		
Established/Proper Name: Pantoprazole		
Dosage Form: (b) (4) powder in a vial for IV administration		
Strengths: 40 mg		
Applicant: Exela Pharma Sciences		
Date of Receipt: 2 Jun 2016		
PDUFA Goal Date: 7 Jul 2017		Action Goal Date (if different): 7 Jul 2017
RPM: Lawrence Allan		
Proposed Indication(s): Short-term treatment of gastroesophageal reflux disease (GERD) associated w/ a history of erosive esophagitis; Pathological hypersecretion conditions including Zollinger-Ellison syndrome		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES

☐

NO

☒

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 020988 PROTONIX IV (pantoprazole sodium)	Highlights Section 4 – Contraindications Section 5 – Warnings and Precautions Section 6 – Adverse Reactions Section 7 – Drug Interactions Section 8 – Use in Specific Populations Section 10 – Overdosage Section 12 – Clinical Pharmacology Section 13 – Nonclinical Toxicology Section 14 – Clinical Studies Section 17 – Patient Counseling Information

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The sponsor provided a written scientific justification to bridge to NDA 020988 PROTONIX IV (pantoprazole sodium).

The sponsor requested a waiver from conducting bioavailability (BA) studies based on 21 CFR §320.22(b) (1), which states that for certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. However, the criteria for a biowaiver under 21 CFR 320.22(b)(1) is not fully met as the proposed drug and the listed drug formulations do not contain exactly the same inactive ingredient (EDTA is absent in the proposed formulation). Nevertheless, based on 21 CFR 320.24(b)(6), the FDA can rely on any other approach deemed adequate by FDA to establish bioequivalence (bio-bridge) between the listed and proposed drug products. In this case, the Division of Biopharmaceutics determined that 21 CFR 320.24(b)(6), can be applied for the following rationales:

- Pantoprazole Sodium for Injection is a parenteral drug product with completely solubilized pantoprazole sodium intended for administration by intravenous infusion.
- The proposed drug product, Pantoprazole Sodium for Injection (NDA No. 209463), the subject of a new drug application seeking approval, has the same active ingredient, dosage form, route of administration, and indications as the listed drug, Wyeth's PROTONIX® I.V. (pantoprazole sodium) for Injection (NDA No. 020988), .
- The proposed drug product differs from the listed drug only with respect to the inactive ingredient (EDTA) concentration. Based on our scientific understanding of the function of EDTA in the proposed formulation (chelating/ (b) (4)), the absence of EDTA in the proposed product is not expected to alter the pharmacokinetic/bioavailability of pantoprazole

sodium compared to the listed product. Additionally, based on the submitted stability data submitted by the sponsor, the absence of EDTA will not affect the stability of the product (i.e., formation of particulates was not observed).

- The physicochemical properties in Table below show that the two products have similar pH values, and the same osmolality, tonicity, and viscosity.

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 (as per label)	9.8 – 10.2 (based on 24 month stability data for 3 lots XLNF1429, XLNF1431, and XLNF1432)
Osmolarity	310 mOsm/kg	310 mOsm/kg
Tonicity	Isotonic	Isotonic
Viscosity	0.016292 Centistokes	0.016292 Centistokes

In summary, the FDA considered that based on 21 CFR 320.24(b)(6), a scientific bridge has been established between the Exela's proposed drug product and the Listed Drug. Therefore, no biostudy to evaluate the relative bioavailability of the Exela's proposed drug product is necessary.

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- PROTONIX IV (intravenous pantoprazole sodium) for injection

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐
If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
PROTONIX IV (pantoprazole sodium) for injection	020988	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES ☐ NO ☒
If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES ☐ NO ☒
If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES ☐ NO ☒
If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

- d) Discontinued from marketing?

YES ☐ NO ☒

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This product differs from the listed drug with respect to the inactive ingredients that are present in the listed drug. The listed drug contains EDTA and sodium hydroxide. This product’s formulation contains only sodium hydroxide as a pH adjuster.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES** to question #1, proceed to question #12; if you answered **NO** to question #1, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☒ NO ☐

If “NO” to (a) proceed to question #11.

If “YES” to (a), answer (b) and (c) then proceed to question #12.

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☒ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”

If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): There are three PE ANDAs listed in the Orange Book.

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☒

If this application relies only on non product-specific published literature, answer “N/A”

*If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): NDAs 022020, 020987, and multiple ANDAs.

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): Pantoprazole (NDA 020988); 6780881, 7351723, and 8754108

No patents listed ☐ *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 6780881, 7351723, and 8754108

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): 23 Aug 2016

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAWRENCE W ALLAN
06/30/2017

JOYCE A KORVICK
06/30/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Memorandum

Date: June 16, 2017 **Date Consulted:** June 20, 2016

From: Christos Mastroyannis, M.D.,
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS,
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products

Drug: Pantoprazole Sodium Injection

Class: Proton pump inhibitor (PPI)

NDA: 209463

Applicant: Exela Pharma Sciences.

Subject: Labeling review of an initial NDA application to be compliant with PLLR

Indications:

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

Materials Reviewed:

- DPMH consult request dated June 20, 2016, DARRTS Reference ID 3948406
- Pharmacology/Toxicology review of Pantoprazole Sodium IV Injection report. Dinesh C. Gautam, Ph.D. March 7, 2017. DARRTS Reference ID 4065866
- DEPI Review of research articles, Joel L. Weissfeld, MD, MPH, March 6, 2017, DARRTS Reference ID 4064920

Consult Question:

DGIEP is seeking recommendations on Pregnancy and Lactation labeling as per PLLR. The applicant did not submit labeling in PLLR format.

INTRODUCTION

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on June 20, 2016, to provide input for appropriate labeling of the pregnancy and lactation subsections of the Pantoprazole Sodium Injection labeling and to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements.

REGULATORY HISTORY

This Pantoprazole Sodium Injection 505(b)(2) application differs from the reference listed drug (RLD), Protonix NDAs 20987 and 22020, with respect to the inactive ingredients that are present in the RLD. (b) (4)

The RLD product, PROTONIX® IV, contains edetate disodium (chelating agent) (u) (u) and sodium hydroxide (pH adjuster). The proposed formulation contains only sodium hydroxide as a pH adjuster and does not contain edetate disodium. The Applicant did not submit any nonclinical or clinical studies for pantoprazole in this NDA. The Applicant relied on the Agency's findings of the safety and efficacy of the RLD product.

Protonix (pantoprazole sodium tablets), NDA 20987, was approved February 2, 2000, and Protonix (pantoprazole sodium delayed-release tablets for delayed-release oral suspension), NDA 222020, was approved on November 14, 2007.

Protonix (pantoprazole for injection) is indicated for:

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

On October 10, 2013, the Agency notified Wyeth Pharmaceuticals, Inc., the manufacturer of the RLD, about new safety information regarding changes in bone morphology and physeal dysplasia observed with another proton pump inhibitor (PPI) in rats exposed prenatally and during lactation. The Agency required an additional postmarketing nonclinical study with pantoprazole sodium to address these safety concerns.

The results of the PMR were submitted to the Agency on November 25, 2015 and DGIEP is requiring safety labeling changes for all pantoprazole-containing products based on these new animal findings.

BACKGROUND

Drug Characteristics^{1,2,3}

Pantoprazole Sodium for Injection, a PPI, is a compound that inhibits gastric acid secretion. It 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. The binding to the (H⁺, K⁺)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours. The stability of the compound in aqueous solution is pH- dependent. The rate of degradation increases with decreasing pH. Pantoprazole is metabolized by cytochrome P450 (CYP2C19 and CYP3A4) to inactive metabolites.

The elimination half-life is about 1 hour but 3-10.0 hours for patients with altered metabolism (slow metabolizers). It binds to albumin by about 98%. The molecular weight is (b) (4) Daltons (432 Daltons for the hydrated form).

It is not known, if it crosses the placenta, but omeprazole with similar drug characteristics does cross the placenta. Because of the short half-life and being degradable in the stomach pH, it is expected that very small amount may pass to the fetus. Higher amounts are anticipated to cross the placenta in slow metabolizers.

Disease Background

Gastro-esophageal reflux and Pregnancy⁴

GERD is seen in about 30-50% of pregnant women and is typically of new onset. The pathogenesis of GERD during pregnancy is controversial. One mechanism by which GERD occurs involves a decrease in the lower esophageal sphincter tone due to the elevated levels of estrogen and progesterone. Other mechanisms by which GERD occurs involve an increase in abdominal pressure due to the enlarged gravid uterus and a decrease in the gastrointestinal transit time during pregnancy.

Mild cases of GERD can be managed with dietary and lifestyle changes; however, moderate to severe cases of GERD may require drug therapy. If lifestyle changes do not work, non-systemically absorbed medications, such as aluminum-, magnesium-, and calcium-containing antacids or sucralfate are used. If antacids or sucralfate do not work, histamine H₂ receptor antagonists (avoiding nizatidine) or prokinetic drugs (metoclopramide, cisapride) are used for patients with more severe symptoms.

¹ Proposed Pantoprazole Sodium Injection labeling Sections 11-Description and 12-Clinical Pharmacology

² Briggs G Gerald, Freeman K Roger, Yaffe J Summer: Drugs in Pregnancy and Lactation, Eighth Edition, 2008 by Lippincott Williams and Wilkins, Philadelphia PA

³ Currently approved Protonix (pantoprazole) labeling. Drugs@FDA, October 24, 2016.

⁴ DPMH Review of Nexium (esomeprazole sodium), Prilosec (omeprazole), Zegerid (omeprazole/sodium bicarbonate) and Vimovo (naproxen/esomeprazole). Carrie Ceresa, PharmD, MPH. November 7, 2013. DARRTS Reference ID 3403670.

Nonclinical Team Review of PMR results⁵

A pre- and postnatal developmental toxicity study of pantoprazole sodium administered orally to rats was performed by the applicant of the RLD. The nonclinical team summarized the following key study findings:

- There were no treatment-related findings in F0 maternal animals at up to 30 mg/kg/day PF-05208751.
- During the pre-weaning dosing phase (PND 4 – 21) of the F1 generation, an increase in mortality and/or moribundity occurred in males at 30 mg/kg/day and females at ≥ 5 mg/kg/day, and there were decreases in body weight and body weight gain in both sexes at ≥ 5 mg/kg/day (compared to controls).
- On PND 21, decreased mean femur length and weight and changes in femur bone mass and geometry were observed at ≥ 5 mg/kg/day (compared to controls). Effects at the femur metaphysis included lower total area, bone mineral content (BMC), and bone mineral density (BMD). At the femur diaphysis, effects included lower total area, periosteal and endosteal circumference, and cross-sectional moment of inertia (CSMI).
- On PND 70, findings were limited to lower femur metaphysis cortical/subcortical BMD in F1 females (compared to controls) at ≥ 5 mg/kg/day (a finding that was not observed in F1 females on PND 21).
- Microscopic evaluation of the distal femur, proximal tibia, and stifle joints revealed no treatment-related changes on either PND 21 or 70.

The study report states that changes in bone parameters were considered secondary to lower body weights. In consultation with the Division of Bone, Reproductive, and Urologic Products (DBRUP), it was concluded that it is possible that the bone effect be secondary to the body weight effect (caused by decreased muscle or fat mass); or the two effects may be due to a common drug-related toxicity.

The reader is referred to the Nonclinical Review by Tracy Behrsing, PhD for further details.

Pregnancy and Lactation Labeling Rule (PLLR)

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*”⁶ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule⁷ format to include information about the risks and benefits of using these products during pregnancy and lactation.

⁵ Pharmacology/Toxicology review of the Protonix (pantoprazole) PMR Final Study Report. Tracy Behrsing, PhD April 13, 2016. DARRTS Reference ID391652

⁶ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

⁷ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

DPMH'S REVIEW OF PUBLISHED LITERATURE REGARDING PANTOPRAZOLE AND USE DURING PREGNANCY

Pregnancy

Nonclinical experience

The proposed labeling as edited by the nonclinical team states:

“Reproduction studies have been performed in rats at intravenous doses up to 20 mg/kg/day (4 times the recommended human dose (b) (4) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose (b) (4) with administration of pantoprazole during organogenesis in pregnant animals and have revealed no evidence of (b) (4) harm to the fetus due to pantoprazole.

A pre- and postnatal development toxicity study in rats with additional endpoints to evaluate the effect on bone development was performed with pantoprazole sodium. Oral pantoprazole doses of 5, 15, and 30 mg/kg/day (approximately 1, 3, and 6 times the human dose of 40 mg/day (b) (4) were administered to pregnant females from gestation day (GD) 6 through lactation day (LD) 21. (b) (4)



There were no effects on fertility or reproductive performance when pantoprazole was given at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area).

In addition the Protonix labeling states:

Reproduction studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.

Human Experience

A review of published literature in PubMed and MicroMedex was conducted by DPMH to evaluate the use of pantoprazole and other PPIs in pregnant women. These studies are summarized below.

In a retrospective cohort study (Matok, *et al.*), a computerized database was created by linking a computerized database of medications dispensed from 1998 to 2009 to all women registered in "Clalit" HMO, southern district of Israel, with computerized databases containing maternal and infant hospitalization records from the district hospital. The authors analyzed the rates of congenital malformations between women exposed to PPIs and women unexposed to PPIs during pregnancy. Overall, 114,960 infants were born during the study period, and 1,239 women had medical pregnancy terminations, of which 468 were performed due to fetal malformations. A total of 1,186 infants and aborted fetuses had been exposed to PPIs during the first trimester of pregnancy. Exposure to PPIs in the first trimester was not associated with an increased risk of congenital malformations (adjusted OR 1.06; 95% CI = 0.84-1.33). In addition, exposure to PPIs during the third trimester of pregnancy was not associated with increased risk of perinatal mortality, premature delivery, low birth weight, or low Apgar scores.⁸

A cohort study was conducted in Denmark between January 1996 and September 2008 (Pasternak, *et al.*), and among 840,968 live births, there were 5,082 live births exposed to PPIs between four weeks before conception and the end of the first trimester of pregnancy. There were 174 major birth defects in infants whose mothers had been exposed to a PPI (3.4%) compared to a 2.6% rate of major birth defects observed in the general population. The following results were observed in women exposed to pantoprazole:

- Of the 392 women who had taken pantoprazole during the one to four weeks before conception, there were 13 major birth defects (3.3%, Adjusted OR 1.28, 95% CI 0.74-2.22).
- Of the 549 women who had taken pantoprazole during the first trimester, there were 21 major birth defects (3.9%, Adjusted OR 1.33, 95% CI 0.85-2.08).
- Of the 325 women who had taken pantoprazole during the second and third trimesters, there were 13 major birth defects (4%, Adjusted OR 1.39, 95% CI 0.79-2.44).

The authors concluded that the rate of birth defects was not significantly increased in secondary analysis of exposure to individual PPIs during the first trimester or in an analysis that limited the offspring of women who had filled their PPI prescription.⁹

A 2002 study, a meta-analysis, studied the use of PPIs in pregnancy. 593 infants exposed to omeprazole, lansoprazole and pantoprazole. The relative risk (RR) for major malformations was 1.18, 95% CI was 0.72-1.94.¹⁰

⁸ Matok, et al. The safety of fetal exposure to proton-pump inhibitors during pregnancy. *Digestive Diseases & Sciences*. 2012. 57 (3): 699-705.

⁹ Pasternak, et al. Use of Proton-Pump Inhibitors in Early Pregnancy and the Risk of Birth Defects. *The New England Journal of Medicine*. 2010

Nikfar S, Abdollahi M, Moretti M et. al.: Use of PPIs during pregnancy and rates of major malformations;; 363(22):2114-2123.

¹⁰ Nikfar S, Abdollahi M, Moretti M et. al.: Use of PPIs during pregnancy and rates of major malformations: a meta-analysis. *Dig Dis Sci* 2002;47:1526-9

A 2005 study by the European Network of Teratology Information Services reported pregnancy outcomes of pregnancies exposed to omeprazole (n=295), lansoprazole (n=62) and pantoprazole (n=53). The median duration for pantoprazole treatment 40 mg/day was 14 days (7-23 days). Outcomes included 1 spontaneous abortion, 3 elective abortions (none for congenital anomalies), 1 stillbirth and 48 live births. Compared to non-exposed control, there was no difference in major malformations (RR 0.55, 95% CI 0.8-3.95).¹¹

Other studies have also demonstrated the safety of omeprazole, lansoprazole, and pantoprazole^{12,13,14,15,16} with no association between exposure to these PPIs during the period of organogenesis and increased risk for major malformations, increased risk of spontaneous abortions, decreased birth weight or perinatal complications.

DPMH^{17,18,19,20,21,22,23,24,25} and the Office of Surveillance and Epidemiology²⁶ have conducted reviews of different PPIs.

Reviewer Comment:

Although there are no adequate and well-controlled studies that have been done with pantoprazole and pregnant women, there are several published post-marketing studies that have been performed in pregnant women taking pantoprazole and other PPIs and no fetal

¹¹ Kallen BA. Use of omeprazole during pregnancy- no hazard demonstrated in 95 infants exposed during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2001; 96: 63-68.

¹² Lalkin et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. Am J Obstet Gynecol 1998;179:727-730

¹³ Diav-Citrin, et al. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. Aliment Pharmacol Ther 2005;21:269-275.

¹⁴ Nielsen, et al. The safety of proton pump inhibitors in pregnancy. Aliment Pharmacol Ther. 1999;13:1085 – 1089.

¹⁵ Kallen B. Delivery outcome after the use of acid-suppressing drugs in early pregnancy with special reference to omeprazole. Br J Obstet Gynaecol. 1998;105:877-881

¹⁶ Wilton et al. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. Br J Obstet Gynaecol. 1998; 105: 882-889.

¹⁷ DPMH Review of Esomeprazole Strontium. Jeanine Best, MSN, RN, PNP. April 23, 2013. DARRTS Reference ID 3297426.

¹⁸ DPMH Review of Nexium (esomeprazole sodium), Prilosec (omeprazole), Zegerid (omeprazole/sodium bicarbonate) and Vimovo (naproxen/esomeprazole). Carrie Ceresa, PharmD, MPH. November 7, 2013. DARRTS Reference ID 3403670.

¹⁹ DPMH Review of Aciphex (rabeprazole sodium). Carrie Ceresa, PharmD, MPH. April 10, 2015. DARRTS Reference ID 3729478

²⁰ DPMH Review of Dexilant (dexlansoprazole). Miriam Dinatale, D.O. November 27, 2015. DARRTS Reference ID 3852781

²¹ DPMH Review of Prilosec (omeprazole magnesium), Christos Mastroyannis, MD. December 23, 2015. DARRTS Reference ID 3873309.

²² DPMH Review of Yosprala (aspirin/omeprazole) Christos Mastroyannis, MD. August 3, 2015.

²³ DPMH review. Prilosec (omeprazole magnesium) delayed-release oral suspension, NDA 022056. Christos Mastroyannis, M.D. January 15, 2016. DARRTS Reference ID 3873309.

²⁴ Vimovo (naproxen/esomeprazole) delayed-release tablets. NDA 22511/s-018. Christos Mastroyannis, M.D. March 2, 2016. DARRTS Reference ID 3900270

²⁵ DPMH review, Protonix (pantoprazole sodium) NDAs: 22020 and 20987, Miriam Dinatale, D.O., November 25, 2016. DARRTS Reference ID 4013263

²⁶ Cambell R. Epidemiology: Literature Review, DARRTS, January 15, 2014 Reference ID: 3435725

malformations, miscarriages or other adverse maternal and/or fetal outcomes have been observed. Therefore, based on the available clinical data, the known risk to the embryo/fetus for developmental toxicity appears to be low. However, these studies are limited due to retrospective study design and some had small sample size.

Summary

The available data from published observational studies failed to demonstrate an association of adverse pregnancy-related outcomes and pantoprazole use.

Methodological limitations of these observational studies cannot definitely establish or exclude any drug-associated risk during pregnancy.

Lactation

Nonclinical experience

Pantoprazole and its metabolites are present in the milk of rats.

Human experience

There is very limited information on pantoprazole and its presence in human milk, the effects on the breastfed infant or on milk production. Both Plante *et. al.* in “Excretion of pantoprazole in human breast milk” and Briggs *et. al.* in “Drugs in Pregnancy and Lactation” present a 43 year-old mother (with a 10 month-old and 8.2 kg healthy female infant) who was given 40 mg pantoprazole tablet.^{2,27} Maternal serum and breast milk were collected over a 24 hour period. Pantoprazole was detected only in the 2 and 4 hours samples (0.036 and 0.24 mcg/m; respectively). After 4 hours, it was undetectable. The milk AUC was about 2.8% of the AUC for plasma. The peak maternal plasma concentration was 1.65 mcg/ml at 2 hours, thus giving a milk-to-plasma ratio of 0.022. The authors calculated that the infant dose would have been ≤0.14% of the weight –adjusted maternal dose. They also suggested that the infant, if she had been breastfeeding, would have been exposed to even less amount of the drug, because pantoprazole is unstable to acid pH in the stomach.

DPMH conducted a search of Medications and Mother’s Milk²⁸, the Drugs and Lactation Database (LactMed)²⁹, Micromedex³⁰, and of published literature in PubMed using the search terms “pantoprazole and lactation,” “pantoprazole and breastfeeding”. No additional reports of clinical lactation studies or case reports of pantoprazole use in lactating women were found in published literature. LactMed states: “pantoprazole

²⁷ Plante L, Ferron GM, Unruh M, Mayer PR. Excretion of pantoprazole in human breast milk.. J Reprod Med 2004;49:825-27

²⁸ Hale, Thomas (2012) Medications and Mothers’ Milk. Amarillo, Texas Hale Publishing

²⁹ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

³⁰ Truven Health Analytics information, <http://www.micromedexsolutions.com/>.

doses of 40 mg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants”.

Reviewer’s comment

This reviewer agrees with the above statement that pantoprazole poses a limited risk to the breastfed infant and as such breastfeeding should not be discouraged. The clinical importance of this finding (very low exposure of the breastfed infant to pantoprazole) is not known.

Summary

Pantoprazole was present in the milk of rats. Because only limited lactation information for pantoprazole exists, the following statement should be included in the risk summary of the labeling: “The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for pantoprazole and any potential adverse effects on the breastfed child from pantoprazole or from the underlying maternal condition.”

Females and Males of Reproductive Potential

According to the product labeling, pantoprazole did not produce adverse effects on fertility in male or female rats given 500 and 450 mg/kg/day, respectively.³¹ In an electronic medical record study, men attempting to conceive a child, and who had a total motile sperm count of 1 million/ejaculate or less, were more likely to have been prescribed a proton pump inhibitor 6-12 months prior to semen analysis than men with a count of more than 1 million/ejaculate.³² There was no association with prescription 0-6 months prior to semen analysis, detracting from the plausibility of the findings.

Summary

Because of limited human data available on the effect of pantoprazole on fertility and no evidence of infertility to inform a potential clinical risk, Section 8.3, Females and Males of Reproductive Potential, will not be included in pantoprazole labeling.

DISCUSSION –Asthma and Allergies and Prenatal Use of PPIs

In the submission for NDA 209463 for pantoprazole sodium IV infusion, Exela Pharma Sciences submitted two published articles to support product labeling under the Pregnancy and Lactation Labeling Rule (PLLR). Using these two articles, Exela submitted a draft label that added information about asthma and allergic disease in offspring of mothers exposed to PPI or histamine-2 receptor antagonists (H2RA)during pregnancy.

³¹ Pantoprazole Sodium tablet, delayed release, January 17, 2015

³² Huijgen NA, de Ridder MAJ, Verhamme KM, Dohle GR, Vanrolleghem AM, Sturkenboom CJM, Laven JSE, Steegers-Theunissen RPM. Are proton-pump inhibitors harmful for the semen quality of men in couples who are planning pregnancy? Fertil Steril 2016;106(7):1666-1672.

DGIEP consulted the Division of Epidemiology I (DEPI) to reviewed the medical literature for information about childhood asthma or allergy from prenatal exposure to PPI or H2RA. DEPI reviewed these two publications plus an additional 6 and concluded 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. Therefore, this weak evidence should be carefully considered by the Division in deciding if this evidence should be included in the labeling as a class effect of prenatal administration of PPIs and childhood allergy. The reader is referred to the review by Joel L. Weissfeld, MD MPH.³³

CONCLUSIONS

DPMH attended labeling meetings with DGIEP during January 30, 2017, February 7, 2017, and May 16, 2017. Discussion was held regarding updating the labeling language with the new animal data from the RLD.

The Pregnancy and Lactation, sections of pantoprazole labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” section of pantoprazole labeling was formatted in the PLLR format to include: “Risk Summary”, and “Data” sections.
- **Lactation, Section 8.2**
 - The “Lactation” section of pantoprazole labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” sections.
- **Females and Males of Reproductive Potential, Section 8.3**
 - Females and Males of Reproductive Potential, Section 8.3 is omitted because there is nothing to be reported.
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of labeling was updated to correspond with sections 8.1 and, 8.2 of labeling.

³³ DEPI review of Gastric Acid Suppression during Pregnancy and Risk of Childhood Allergy by Joel L. Weissfeld, MD MPH in DARRTS, Dated March 6, 2017, Reference ID 4064920

DPMH LABELING RECOMMENDATIONS

DPMH Proposed Pantoprazole Sodium Pregnancy Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- **Pregnancy:** Based on animal data, may cause fetal harm (8.1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published observational studies did not demonstrate an association of major malformations or other adverse pregnancy outcomes with pantoprazole [see Data].

In animal reproduction studies, no evidence of adverse development outcomes was observed with pantoprazole. Reproduction studies have been performed in rats at intravenous doses up to 20 mg/kg/day (4 times the recommended human dose) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose) with administration of pantoprazole during organogenesis in pregnant animals and have revealed no evidence of harm to the fetus due to pantoprazole in this study [see Data].

A pre- and postnatal development toxicity study in rats with additional endpoints to evaluate the effect on bone development was performed with pantoprazole sodium. Oral doses of 5, 15, and 30 mg/kg/day (approximately 1, 3, and 6 times the human dose of 40 mg/day) were administered to pregnant females from gestation day (GD) 6 through lactation day (LD) 21. Changes in bone morphology were observed in pups exposed to pantoprazole *in utero* and through milk during the period of lactation as well as by oral dosing from postnatal day (PND) 4 through PND 21 [see Use in Specific Populations (8.4)]. There were no drug-related findings in maternal animals. Advise pregnant women of the potential risk to fetal bone development.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data:

Available data from published observational studies failed to demonstrate an association of adverse pregnancy-related outcomes and pantoprazole use. Methodological limitations of these observational studies cannot definitely establish or exclude any drug-associated risk during pregnancy. In a prospective study by the European Network of Teratology Information Services, outcomes from a group of 53 pregnant women administered median daily doses of 40 mg pantoprazole were compared to a control group of 868 pregnant women who did not take any proton pump inhibitors (PPIs). There was no difference in the rate of major malformations between women exposed to PPIs and the control group, corresponding to a Relative Risk (RR)= 0.55, [95% Confidence Interval (CI) 0.08-3.95]. In a population-based retrospective cohort study covering all live births in Denmark from 1996 to 2008, there was no significant increase in major birth defects during analysis of first trimester exposure to pantoprazole in 549 live births. A meta-analysis that compared 1,530 pregnant women exposed to PPIs in at least the first trimester with 133,410 unexposed pregnant women showed no significant increases in risk for congenital malformations or spontaneous abortion with exposure to PPIs (for major malformations OR=1.12 ([95% CI 0.86-1.45] and for spontaneous abortions OR=1.29 [95% CI 0.84-1.97]).

Animal Data

Reproduction studies have been performed in rats at intravenous doses up to 20 mg/kg/day (4 times the recommended human dose based on body surface area) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose based on body surface area) with administration of pantoprazole during organogenesis in pregnant animals and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.

A pre- and postnatal development toxicity study in rats with additional endpoints to evaluate the effect on bone development was performed with pantoprazole sodium. Oral pantoprazole doses of 5, 15, and 30 mg/kg/day (approximately 1, 3, and 6 times the human dose of 40 mg/day on a body surface area basis) were administered to pregnant females from gestation day (GD) 6 through lactation day (LD) 21. On postnatal day (PND 4) through PND 21, the pups were administered oral doses at 5, 15, and 30 mg/kg/day (approximately 1, 2.3, and 3.2 times the exposure (AUC) in children aged 6 to 11 years at a dose of 40 mg (6.9 mcg.h/mL)). There were no drug-related findings in maternal animals. During the preweaning dosing phase (PND 4 to 21) of the pups, there were increased mortality and/or moribundity and decreased body weight and body weight gain at 5 mg/kg/day (approximately equal exposures (AUC) in children receiving the 40 mg dose) and higher doses. On PND 21, decreased mean femur length and weight and changes in femur bone mass and geometry were observed in the offspring at 5 mg/kg/day (approximately equal exposures (AUC) in children at the 40 mg dose) and higher doses. The femur findings included lower total area, bone mineral content and density, periosteal and endosteal circumference, and cross-sectional moment of inertia. There were no microscopic changes in the distal femur, proximal tibia, or stifle joints. Changes in bone parameters were partially reversible following a recovery period, with findings on PND 70 limited to lower femur metaphysis cortical/subcortical bone mineral density in female pups at 5 mg/kg/day (approximately equal exposures (AUC) in children at the 40 mg dose) and higher doses.

8.2 Lactation

Risk Summary

The limited data from a single case reports the presence of pantoprazole in human breast milk. There were no effects on the breastfed infant [see Data]. There are no data on pantoprazole effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for pantoprazole and any potential adverse effects on the breastfed child from pantoprazole or from the underlying maternal condition.

Data

The breast milk of a 42-year-old woman receiving 40 mg of oral pantoprazole, at 10 months postpartum, was studied for 24 hours, to demonstrate low levels of pantoprazole present in the breast milk. Pantoprazole was detectable in milk only 2 and 4 hours after the dose with milk levels of approximately 36 mcg/L and 24 mcg/L, respectively. A milk-to-plasma ratio of 0.022 was observed at 2 hours after drug administration. Pantoprazole was not detectable (<10 mcg/L) in milk at 6, 8 and 24 hours after the dose. The relative dose to the infant was estimated to be 7.3 mcg of pantoprazole, which is equivalent to 0.14% of the weight-adjusted maternal dose. No adverse events in the infant were reported by the mother.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise a pregnant woman of the potential risk to a fetus. Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy [see *Use in Specific Populations (8.1)*].

**Appendix A: Currently Approved PROTONIX I.V.- pantoprazole sodium injection,
powder, for solution by Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.
Pantoprazole Pregnancy Labeling, April 20, 2017**

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)



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/s/

CHRISTOS MASTROYANNIS
06/16/2017

TAMARA N JOHNSON
06/16/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: May 24, 2017

To: Lawrence Allan
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 209463
OPDP Comments for proposed draft PI for PANTOPRAZOLE SODIUM
for injection, for intravenous use

OPDP has reviewed the proposed draft PI for pantoprazole sodium. We have no additional comments.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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MEMORANDUM TO FILE

Pediatric Labeling Review

From: Amy M. Taylor, MD, MHS Medical Officer
Division of Pediatric and Maternal Health

Through: Hari Cheryl Sachs, MD, Team Leader
Division of Pediatric and Maternal Health

John J. Alexander, MD, MPH Deputy Director
Division of Pediatric and Maternal Health

NDA Number: 209-463

Sponsor: Exela Pharma Sciences

Drug: Pantoprazole sodium

**Dosage Form and
Route of Administration:** Injectable

**Sponsor Proposed
Indications:**

- 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 in adults.

Consult Request: The Division of Gastroenterology and Inborn Error Products (DGIEP) requests DPMH's input on the proposed labeling for pantoprazole sodium. In addition, the sponsor has requested a pediatric waiver. DGIEP asks DPMH to evaluate whether the waiver is applicable.

Background

The sponsor submitted a 505(b)(2) application for pantoprazole sodium for injection on June 2, 2016. Included in the application is a request for a full waiver of pediatric studies. The sponsor states that the “proposed drug product has the same active ingredient, and same indication, dosage form, dosing regimen, and route of administration as that of the reference drug, Protonix® I.V. (pantoprazole sodium).”

Reviewer comment: Since the product does not trigger PREA, there is no need to request a full waiver of pediatric studies under PREA.

Reference Drug

Protonix® I.V. (pantoprazole sodium) for injection was originally approved in March 22, 2001 for short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD). Protonix® I.V. is not approved in pediatric patients. The original approval letter stated that FDA was deferring submission of the pediatric study reports until April 1, 2004. Later that year, when the indication for hypersecretory conditions, including Zollinger-Ellison Syndrome was approved on October 19, 2001, the approval letter stated that a waiver of pediatric studies had been granted for that indication. On December 6, 2004, Protonix® I.V. was approved for the short-term treatment of patients with gastroesophageal reflux disease and a history of erosive esophagitis. The product was granted a deferral of a pediatric study for the treatment of GERD in pediatric patients aged 0 to 16 years. The final report submission was due July 19, 2009. Protonix® I.V. continues to have a post-marketing requirement of a pediatric study for the short-term treatment of GERD in patients 0 to 16 years. The current status is delayed. The sponsor requested a deferral extension on January 4, 2013 which was denied.

Of note, the reference drug, Protonix®, recently submitted the results of a nonclinical pre- and post-natal study with a focus on bone toxicity. (b) (4)

Sponsor proposed labeling with suggested edits (strikethroughs represent deletions and underlining represents additions)

Reviewer comment: The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

8.4 Pediatric Use

Safety and effectiveness of Pantoprazole Sodium for Injection in pediatric patients have not been established.

Animal Toxicity Data

(b) (4)

In a pre- and post-natal development study in rats, the pups were administered oral doses of pantoprazole at 5, 15, and 30 mg/kg/day on postnatal day (PND) 4 through PND 21, in addition to lactational exposure through milk. On PND 21, decreased mean femur length and weight and changes in femur bone mass and geometry were observed in the offspring at 5 mg/kg/day and higher doses. Changes in bone parameters were partially reversible following a recovery period [see Use in Specific Populations (8.1)].

In neonatal/juvenile (b) (4) (rats and dogs) toxicities were similar to those observed in adult animals, including gastric alterations, decreases in red cell mass, increases in lipids, enzyme induction and hepatocellular hypertrophy. Increased incidence of eosinophilic chief cells in adult and neonatal/juvenile rats, and atrophy of chief cells in adult rats and in neonatal/juvenile dogs, were observed in the fundic mucosa of stomachs in repeat-dose studies. Full to partial recovery of these effects were noted in animals of both age groups following a recovery period.

Reviewer comment: Information on animal toxicity should be moved from subsection 13.2 to subsection 8.4 per new labeling policy. In addition, changes to the Protonix® labeling which are planned based on the results of the nonclinical pre- and post-natal study with a focus on bone toxicity should be incorporated into this labeling as well.

(b) (4)

Reviewer comment: Please see above reviewer comment. Edits were made to the information in subsection 13.2 as it was moved to subsection 8.4 in order to provide information on animal toxicity that is clinically relevant.

Recommendations

Since the product does not trigger PREA, there is no need to request a full waiver of pediatric studies under PREA.

Information on juvenile animal toxicity should be moved from subsection 13.2 to subsection 8.4 per new labeling policy. The information in subsection 13.2 was moved to

subsection 8.4, and edited in order to provide information on animal toxicity that is clinically relevant.

(b) (4)



Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations (see approval letter).

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/s/

AMY M TAYLOR
03/23/2017

HARI C SACHS
03/23/2017

JOHN J ALEXANDER
03/23/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)
Epidemiology: Review of Research Articles**

Date: March 6, 2017

Reviewer(s): Joel L. Weissfeld, MD MPH
Division of Epidemiology I

Acting Team Leader: Kira Leishear White, PhD, MS
Division of Epidemiology I

Acting Associate Director: Lockwood Taylor, PhD
Division of Epidemiology I

Drug Name(s): Pantoprazole (Protonix)

Subject: Gastric Acid Suppression during Pregnancy and Risk of
Childhood Allergy

Application Type/Number: NDA 209463

Applicant/sponsor: Exela Pharma Sciences

OSE RCM #: 2017-291

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EXECUTIVE SUMMARY

To help the Division of Gastroenterology and Inborn Error Products (DGIEP) properly label drugs used to suppress gastric acid, the Division of Epidemiology I (DEPI) reviewed the medical literature for information about childhood asthma or allergy from prenatal exposure to proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2RA).

In NDA 209463 for pantoprazole sodium IV infusion, Exela Pharma Sciences submitted two published articles to support product labeling under the Pregnancy and Lactation Labeling Rule (PLLR). [REDACTED] (b) (4)

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 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.

DEPI recommended that DGIEP consider the weak evidence for causality [REDACTED] (b) (4)

1. INTRODUCTION

1.1 Background

To help the Division of Gastroenterology and Inborn Error Products (DGIEP) properly label drugs used to suppress gastric acid, the Division of Epidemiology I (DEPI) reviewed the medical literature for information about childhood asthma or allergy from prenatal exposure to proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2RA).

In NDA 209463 for pantoprazole sodium IV infusion, Exela Pharma Sciences submitted two published articles [1, 2] [REDACTED] (b) (4)

[REDACTED] DGIEP asked DEPI to provide an opinion about these two articles. (See ATTACHMENT 1 for the verbatim consult request from DGIEP to the Office of Surveillance and Epidemiology, OSE) To provide satisfactory feedback, DEPI completed a rapid review of literature about childhood asthma or allergy from prenatal exposure to PPI or H2RA.

1.2. Regulatory History

Date	Event
July 7, 2016	Exela Pharma Sciences submits NDA 209463 for pantoprazole sodium IV infusion
November 30, 2016	Exela Pharma Sciences submits draft PLLR labeling (b) (4)
February 9, 2017	DGIEP asks DEPI for comment about Anderson 2012 [1] and Mulder 2014 [2]

2. REVIEW METHODS AND MATERIALS

Date	Source	Document
July 6, 2012	DEPI	Literature Review about Omeprazole in Pregnancy
January 15, 2014	DEPI	Literature Review about Proton Pump Inhibition and Congenital Malformation
December 11, 2014	DEPI	Literature Review about Histamine-2 Receptor Antagonists in Pregnancy
April 16, 2015	DPMH	PLLR Review for Rabeprazole Sodium
November 30, 2015	DPMH	PLLR Review for Dexlansoprazole
January 15, 2016	DPMH	PLLR Review for Omeprazole
August 15, 2016	Exela Pharma	Literature Review for PLLR
November 15, 2016	DPMH	PLLR Review for Omeprazole and Esomeprazole
November 30, 2016	Exela Pharma	Literature Review (b) (4)

To complement the two articles [1, 2] submitted by Exela, DEPI conducted a search of medical literature for articles about childhood asthma or allergy from prenatal exposure to proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2RA).¹

The following MESH-based PubMed search, completed on February 12, identified 44 articles.

(((((Gastrointestinal Agents[MeSH Terms])) OR Histamine H2 Antagonists[MeSH

¹ On February 13, Joette Meyer, on behalf of DGIEP, accepted a DEPI recommendation for expanding the review scope to include a search for other informative articles in literature, to complement the two articles submitted by Exela Pharma.

Terms)) OR Proton Pump Inhibitors[MeSH Terms])) AND Prenatal Exposure Delayed Effects[MeSH Terms])

A Web of Science search for articles citing **Dehlink 2009** [3] identified another 28 articles. Recently published articles pointed to **Dehlink 2009** as the foundation article about allergy in children from prenatal exposure to drugs used to suppress gastric acid.

DEPI examined the titles and abstracts of the 72 articles identified by electronic bibliographic search to find five articles for review [3-7], in addition to the two articles submitted by Exela. DEPI discovered an eighth article [8] in the reference lists of other articles selected for review.

3. REVIEW RESULTS

3.1 Study Overviews

ATTACHMENT 2 contains tabular summaries of the eight articles covered by this review.

3.1.1 Health Registers of the Swedish National Board of Health and Welfare

Dehlink 2009 [3] used the Swedish Medical Birth Register to define a population-based cohort of vaginal-birth term infants (N=585,716), born between 1995 and 2004 to fertile mothers cohabitating with a father. Dehlink used (1) the Medical Birth Register to define prenatal exposures to drugs in the Anatomical Therapeutic Chemical (ATC) A02B class (Drugs for Peptic Ulcer and Gastro-Oesophageal Reflux Disease), (2) 1995-2006 Hospital Discharge Register to identify childhood hospitalization for allergic diseases, and (3) 2005-2006 Prescribed Drug Register to identify childhood prescriptions for asthma medications, steroid ointments, epinephrine auto-injectors, and antihistamines. Dehlink combined childhood hospital diagnosis codes and prescription information to define five types of allergic disease, including asthma, food allergy, atopic dermatitis, allergic rhinitis, and other unspecified allergic reactions or anaphylaxis. The definition for childhood asthma, for example, required >1 hospitalization for asthma (ICD-9 493), hospitalization for asthma after two years of age, or >1 prescriptions for an asthma medication (ATC R03, Drugs for Obstructive Airway Diseases). Dehlink expressed associations between prenatal exposures and childhood outcomes by the Mantel-Haenszel odds ratio (OR), adjusted for year of birth and for maternal age, parity, smoking, and body mass index. Documenting prenatal PPI exposure anytime during pregnancy in 2916 children (0.5% of 585,716), including 220 (7.5% of 2916) with allergic diseases, Dehlink estimated the association between prenatal PPI and childhood allergic disease at OR 1.46, 95% confidence interval, CI, 1.27-1.66. Documenting prenatal ATC A02B in 5645 children (1.0% of 585,716), including 318 (5.6% of 5645) with asthma, Dehlink estimated the association between prenatal ATC A02B and childhood asthma at OR 1.51, 95% CI 1.35-1.69. Dehlink did not report the OR for prenatal PPI and childhood asthma.

Källén 2013 [8] used the Swedish Medical Birth Register to define population-based cohorts of infants born between 1999 and 2007. Källén used (1) the Medical Birth Register to define 2nd or 3rd trimester prenatal exposures to drugs for GERD (probably defined by ATC A02B) and to drugs in other ATC classes and (2) 2005-2009 Prescribed Drug Register to identify childhood prescriptions for asthma medications. The definition for childhood asthma required ≥ 5

prescriptions, after the 2nd anniversary of birth, for an asthma medication. Following Dehlink 2009 [3], Källén expressed the association between 2nd or 3rd trimester prenatal exposures and childhood outcomes by the Mantel-Haenszel odds ratio, adjusted for year of birth and for maternal age, parity, smoking, and body mass index. In a birth cohort (N=571,277) that excluded children of mothers with evidence of asthma, Källén identified 2275 children (0.4% of 571,277) with prenatal ATC A02B, including 171 (7.1% of 2275) with asthma. In this cohort, Källén estimated the association between prenatal ATC A02B and childhood asthma at OR 1.32, 95% CI 1.12-1.55. Källén did not report the OR for prenatal PPI and childhood asthma.

3.1.2 University of Groningen Prescription Database for Northern Netherlands

Mulder 2013 [5] used the University of Groningen mother-child linked prescription database for northern Netherlands to identify singleton births, between 1995 and 2006, with ≥ 5.5 years database follow-up. The case group included children (1) with asthma, as defined by ≥ 2 prescriptions for asthma drugs (ATC R03) in a 6-month period before age 5 years and (2) a sibling without asthma. One analysis used conditional logistic regression to estimate the relative odds of prenatal exposure to ATC A02B drugs in cases vs. matched siblings. Including 1253 children with asthma (N=48, 3.8%, with prenatal ATC A02B) and 1253 paired siblings without asthma (N=31, 2.5%, with prenatal ATC A02B), this first analysis estimated the association between prenatal ATC A02B and childhood asthma at OR 1.85, 95% CI 1.07-3.19. A second conditional logistic regression analysis compared the same children with asthma to unrelated asthma-free children, matched to the children with asthma according to calendar time and maternal age at delivery. Including 8771 unrelated children without asthma (N=225, 2.6%, with prenatal ATC A02B), this second analysis estimated the association between prenatal ATC A02B and childhood asthma at OR 1.52, 95% CI 1.11-2.10, adjusted for age of the mother at delivery. Mulder did not report the OR for prenatal PPI and childhood asthma.

Mulder 2014 [2], an article cited by Exela to support PLLR labeling, used the University of Groningen mother-child linked prescription database to define a 1995-2011 birth cohort (N=33,536) for northern Netherlands. Mulder used proportional hazards regression to characterize associations between prenatal exposures to H2RA or PPI and onset after birth of atopic dermatitis, asthma, or allergic rhinitis, as defined by ≥ 2 prescriptions within 12 months for steroid or calcineurin inhibitor ointments, inhaled corticosteroids, or nasal steroids, respectively. Mulder observed asthma in 39 of 319 children (12.2%) with prenatal PPI, without prenatal H2RA, and estimated excess asthma risk from prenatal PPI only at hazard ratio, HR, 1.35, 95% CI 0.94-1.94, adjusted for year of birth, sex of child, use of acid-suppressive drugs by child before index date, age of mother at delivery, maternal use of systemic antibiotics during pregnancy, and allergic disease in the mother.

3.1.3 General Practice Research Network (GPRD) for the United Kingdom

Hak 2013 [4] used the United Kingdom General Practice Research Database (GPRD) to identify 0-14 year-old case children with (1) first asthma diagnosis between 1996 and 2010 and (2) a matching control sibling without asthma. Eligibility as a case or control required (1) singleton birth, (2) ≥ 3 years GPRD coverage after birth, and (3) mother with ≥ 12 months GPRD coverage before first completed pregnancy between 15 and 40 years of age. Eligibility as a matching control required presence in “in the database at an age similar to that of the case (± 1 year) at first

diagnosis of asthma.” Hak used conditional logistic regression to characterize associations between prenatal exposures to drugs for gastric acid suppression and asthma, as defined by first diagnosis before age 15 years, if followed within 12 months by ≥ 3 prescriptions for drugs used to treat asthma. Including 1874 children with asthma (N=13, 0.7%, with prenatal PPI) and 1874 paired siblings without asthma (N=7, 0.4%, with prenatal PPI), Hak estimated the association between prenatal PPI and childhood asthma at OR 2.76, 95% CI 0.93-8.17.

3.1.4 Linked Danish Medical Birth Registry for Northern Denmark

Andersen 2012 [1], an article cited by Exela to support PLLR labeling, used the Danish Medical Birth Registry, linked to Aarhus University Prescription Database and Danish National Registry of Patients, to define a 1996-2008 birth cohort (N=197,060) for northern Denmark. Andersen used proportional hazards regression to characterize the association between prenatal exposures to H2RA or PPI and onset after birth of childhood asthma, as defined by a hospital, outpatient, or emergency-room visit for asthma or ≥ 2 prescriptions for a β -agonist and inhaled glucocorticoid. Analysis showed higher asthma risk in N=2238 children with prenatal PPI (HR 1.41, 95% confidence interval, CI, 1.27-1.56), adjusted for year of birth, county of residence, gender of child, gestational age, birth order, mode of delivery, mother’s age at delivery, maternal smoking in pregnancy, maternal use of systemic antibiotics during pregnancy, and maternal history of asthma recorded at any time prior to delivery.

3.1.5 Linked Healthcare Databases for Southern Israel

Yitshak-Sade 2016 [7] used database linkage to define a cohort of N=91,428 2-year old children born between 1999 and 2008 at the Soroka Medical Center in southern Israel to women belonging to the Clalit Health Maintenance Organization. Yitshak-Sade defined childhood asthma by hospitalization for asthma or wheezing or prescription for asthma medications. Yitshak-Sade used generalized estimating equations with Poisson-distributed outcome to measure relative risks (incidence rate ratio, IRR) from prenatal exposures to H2RA or PPI. With 5025 children (5.5%) exposed prenatally PPI or H2RA, Yitshak-Sade estimated excess childhood asthma incidence after two years of age, from prenatal PPI, at IRR 1.10, 95% CI 0.98-1.22, adjusted for birth year, maternal factors (age, allergy, asthma, and infertility treatment), prenatal exposures (antibiotics, nonsteroidal anti-inflammatory drugs, metoclopramide, and insulin), lack of prenatal care, factors determined at birth (sex, preterm birth, cesarean section delivery, and low birth weight), and childhood exposure to H2RA or PPI before 2 years of age.

3.1.6 The Health Improvement Network (THIN) for the United Kingdom

With support from the pharmaceutical industry, **Cea Soriano 2016** [6] used The Health Improvement Network (THIN) in the United Kingdom to define cohorts of 1-year-old children born to matched groups of 18-45 year-old mothers under primary physician care for ≥ 1 year before delivery. Cea Soriano selected a control sample of H2RA and PPI non-exposed mothers, matched to exposed mothers according to calendar quarter of last menstrual period (LMP) and maternal age at LMP. Cea Soriano used proportional hazards regression to characterize, in the offspring of exposed and non-exposed mothers, associations between prenatal exposure to H2RA or PPI and onset after one year of age of asthma, as ascertained by electronic screen of electronic medical records for asthma-related codes and confirmed by manual medical record review

blinded to prenatal exposure histories. Cea Soriano validated asthma occurring after one year of age in 73 of 957 (7.6%) children with prenatal PPI exposure and estimated excess asthma risk from prenatal PPI at HR 1.03, 95% CI 0.76-1.40, adjusted for sex of child, number of maternal primary care physician visits and referrals during the year before LMP through end of pregnancy, maternal comorbidities (asthma, allergies, gastroesophageal reflux disease, and peptic ulcer), and maternal use of non-steroidal anti-inflammatory drugs, antacids, antibiotics, and antihistamines during pregnancy.

3.2 Data Synthesis

DEPI identified five articles [1, 2, 4, 6, 7] with information specific to prenatal PPI or H2RA and childhood asthma. As shown in Figure 1, these articles described asthma occurring more frequently in children with prenatal exposure to PPI than in children without exposure to PPI. Three of four articles with information about both PPI and H2RA reported covariate-adjusted asthma risks greater for prenatal H2RA than prenatal PPI. Two articles published in 2016 [6, 7] reported covariate-adjusted risks closer to one than three articles published earlier [1, 2, 4].

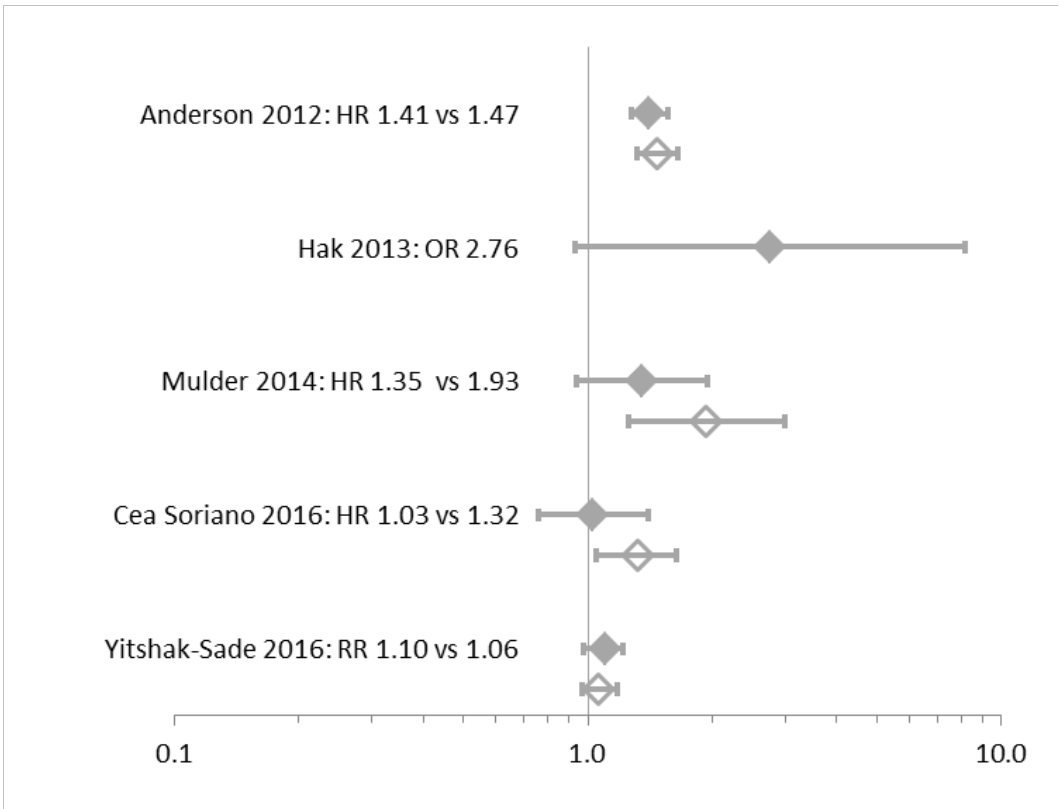


Figure 1: Forest plot of prenatal PPI (filled diamond) or H2RA (unfilled diamond) and childhood asthma, showing study-specific covariate-adjusted effect estimates and 95% confidence intervals, as the hazard ratio (HR), odds ratio (OR), or incidence rate ratio (RR).

DEPI identified two articles [2, 3] with information specific to prenatal PPI or H2RA and

childhood allergic disease, expressed in both articles as a composite that included asthma. As shown in Figure 2, both articles described allergic diseases occurring more frequently in children with prenatal exposure to PPI.[2] One article reported covariate-adjusted risk greater for prenatal H2RA than prenatal PPI. The other article reported covariate-adjusted risk slightly less for prenatal H2RA than prenatal PPI.[3]

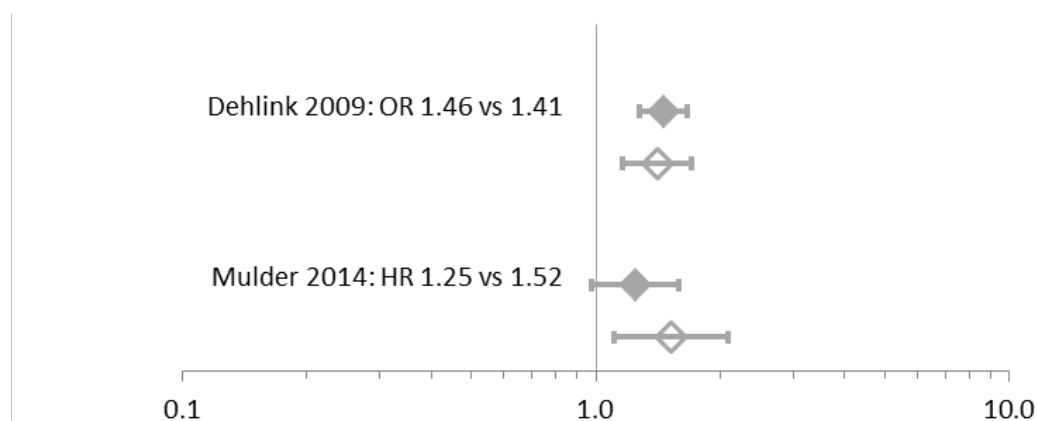


Figure 2: Forest plot of prenatal PPI (filled diamond) or H2RA (unfilled diamond) and childhood allergic disease composite, showing study-specific covariate-adjusted effect estimates and 95% confidence intervals, as the odds ratio (OR) or hazard ratio (HR). Dehlink and Mulder referenced exposures differently. Dehlink referenced prenatal exposure to PPI against prenatal non-exposure to PPI and prenatal exposure to H2RA against prenatal non-exposure to H2RA. Mulder referenced prenatal exposure to PPI and prenatal exposure to H2RA against a common reference, prenatal non-exposure to PPI or H2RA.

4. DISCUSSION

DEPI reviewed eight published articles from epidemiologic studies in six populations with information about associations between prenatal exposures to PPI or H2RA and childhood allergic disease, including asthma. Motivated by human and animal evidence for fetal allergic sensitization possibly related to food allergens not digested by the mother, a foundation article by **Dehlink 2009** [3] combined information in three Swedish health registers to identify a statistically significant association between prenatal PPI and childhood allergic disease. Five studies subsequent to Dehlink measured the covariate-adjusted association between prenatal PPI and childhood asthma (Figure 1). Effect estimates ranged between HR 1.03, 95% CI 0.76-1.40, in an industry-supported study conducted in THIN (**Cea Soriano 2016** [6]), and, OR 2.76, 95% CI 0.93-8.17, in a study conducted in GPRD (**Hak 2013** [4]). A Dutch study (**Mulder 2014** [2]) measured the covariate-adjusted association between prenatal PPI and childhood allergic disease at HR 1.25, 95% CI 0.98-1.59 (Figure 2).

The epidemiology studies found by DEPI used generally accepted methods to estimate independent associations between prenatal exposures and childhood outcomes. Six studies [1-3, 6-8] used cohort designs to measure disease risks in children with prenatal exposure relative to children without prenatal exposure. Two other studies [4, 5] used crossover designs that

arguably achieved better control for factors intrinsic to the mother. On whole, the weight of evidence from these epidemiologic studies supports a possible increase in childhood allergy, including asthma, from prenatal PPI (Figure 1 and Figure 2). In light of the high frequency of childhood asthma and other allergic diseases, a small increase in relative risk could translate into a possible public health burden of legitimate concern.

However, DEPI judged as inadequate the evidence for causal association between prenatal PPI and childhood allergy. Concerns in DEPI included (1) quantitatively weak association (according to standards customarily used in epidemiology to judge causal significance), (2) available evidence not showing childhood risks increasing with higher prenatal dose exposures, (3) nonspecific association extending to include H2RA (Figure 1 and Figure 2), (4) speculative biologic explanation linking prenatal PPI to childhood allergy, and (5) moderate risk of bias due to confounding.

Confounding generally threatens proper interpretation of information from observational studies of prenatal exposures and childhood outcomes. For present purposes, confounding pertains to factors related both to childhood allergy and maternal use of H2RA or PPI for gastroesophageal reflux disease (GERD). Factors known empirically to confound association between prenatal H2RA or PPI and childhood allergy include, (1) maternal asthma or allergy, (2) maternal body mass index, (3) maternal smoking during or after pregnancy, (3) maternal use of systemic antibiotics during pregnancy, (5) cesarean delivery, and (6) preterm birth. All studies covered in this review used methods to mitigate confounding. However, taking stock of the complex of factors plausibly related to childhood allergic disease and maternal use of drugs for symptomatic GERD, the quantitatively weak association (according to epidemiology standard for judging causal significance), and the data limitations common to retrospective epidemiologic investigation, DEPI judged as at least moderate the potential for material bias to interpretation from uncontrolled confounding. Noting plausible association between measures of maternal illness during pregnancy and subsequent illness in offspring, DEPI concluded that results from most studies in this review plausibly exaggerated the true causal association between prenatal PPI and childhood allergic disease.

In addition to confounding, errors measuring exposures and outcomes regularly contribute to the uncertainty of results from epidemiologic studies that rely on data collected retrospectively for reasons unrelated to the research question. In this context, one study (**Cea Soriano 2016 [6]**) used higher quality information available in electronic medical records to determine maternal comorbidities and concomitant drug use during pregnancy and to confirm childhood asthma outcomes. This arguably more rigorously conducted epidemiologic study found no apparent association between prenatal PPI and childhood asthma (HR 1.03, Figure 1). Because of statistical uncertainty (95% CI 0.76-1.40), however, the results from this one study do not necessarily contradict the increase, suggested by the evidence overall, in childhood asthma or allergic disease from prenatal PPI.

This review updates a December 2014 DEPI review of literature about H2RA safety during

pregnancy.² The 2014 DEPI review included two articles [1, 3] also covered in this update. (Please see the 2014 DEPI review for a more thorough discussion of the limitations to epidemiologic study of PPI or H2RA during pregnancy.) Also noting possible childhood asthma risk from prenatal exposure to either PPI or H2RA, the 2014 DEPI review found “inconclusive evidence for causal effect” (b) (4)

5. CONCLUSION

The weight of evidence available from observational studies shows 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 contains very limited evidence for causal association between prenatal exposure to PPI or H2RA and childhood allergy.

6. RECOMMENDATIONS FOR DGIEP

DEPI recommends that DGIEP consider the weak evidence for causality (b) (4)

7. REFERENCES

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² Leishear, K, December 11, 2014, Literature Review of the Safety of H2-receptor Antagonist Use during Pregnancy, Filed under NDA 019462 on December 12, 2104.

7. Yitshak-Sade M, Gorodischer R, Aviram M, Novack L. Prenatal exposure to H2 blockers and to proton pump inhibitors and asthma development in offspring. *J Clin Pharmacol*. 2016 Jan;**56**(1):116-23.
8. Källén B, Finnstrom O, Nygren KG, Otterblad Olausson P. Maternal drug use during pregnancy and asthma risk among children. *Pediatr Allergy Immunol*. 2013 Feb;**24**(1):28-32.

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J Korvick / P Venkataraman / J Meyer / A Rajpal / M Dannis / L Allan (DGIEP)

ATTACHMENT 1: Request for consultation from DGIEP to OSE

We're in the process (b) (4) 505(b)(2) application and request OSE assistance to evaluate and provide their opinion on the validity of two studies referenced (b) (4)

Published, population-based cohort studies from Denmark and the Netherlands demonstrate an association with asthma and allergy development in children exposed to PPIs in utero. A cohort of 197,060 children, born between 1996 and 2008 in northern Denmark, were followed to investigate if proton pump inhibitors (PPIs) may activate the immune system and cause asthma. A total of 24,506 (12.4%) children developed asthma during follow-up (median follow-up = 6.8 years) and 2,238 (1.1%) children were prenatally exposed to PPIs. The adjusted incident rate ratio (aIRR) of asthma associated with prenatal exposure to PPIs was 1.41 [95% confidence interval (CI): 1.27–1.56], compared with those unexposed. The association did not vary by trimester of exposure. Another cohort study was performed using a pregnancy database identifying over 33,536 children in the Netherlands to be analyzed for prenatal exposure to acid suppressive drugs such as PPI's. The study found an increased risk of allergic diseases to the offspring of women with prenatal exposure to PPI's compared to non-exposed children. The adjusted hazard ratio (aHR) for the development of any allergic disease was 1.37 [95% CI: 1.14–1.66] for children exposed to PPIs in utero.

The referenced studies are: **Clinical and Experimental Allergy, v44: pgs 261-69 (2014)** and **Alimentary Pharmacology and Therapeutics, v35: pgs 1190-98 (2012)** and are attached to this consult request.

ATTACHMENT 2: Information from articles about childhood allergic disease from prenatal exposure to drugs used to suppress gastric acid, sorted by year of publication and author.

Part 1: Populations

Author Year	Population and Study Design	Location	Time Period	Data Source
Dehlink 2009	Population-based cohort study of vaginal-birth term infants born to fertile mothers cohabitating with a father	Sweden	1995-2004	Medical Birth Register linked to Hospital Discharge Register and Prescribed Drug Register
Andersen 2012	Population-based cohort study of singletons born alive	Northern Denmark	1996-2008	Danish Medical Birth Registry linked to Aarhus University Prescription Database and Danish National Registry of Patients
Hak 2013	Case-control study of children with asthma matched to siblings without asthma	United Kingdom	1996-2010	General Practice Research Database
Källén 2013	Population-based cohort study of singletons born alive	Sweden	1999-2007	Medical Birth Register linked to Hospital Discharge Register and Prescribed Drug Register
Mulder 2013	Case-control studies of children with asthma matched to siblings (Study #1) or unrelated children (Study #2) without asthma	Northern Netherlands	1995-2006	University of Groningen mother-child linked prescription database
Mulder 2014	Cohort study of singletons born to mothers with ≥ 12 months pharmacy data before date of delivery	Northern Netherlands	1995-2011	University of Groningen mother-child linked prescription database
Cea Soriano 2016	Matched cohort study of 1-year-old children born to 18-45 year-old mothers under THIN PCP care for ≥ 1 year before delivery	United Kingdom	1996-2010	The Health Improvement Network (THIN)
Yitshak-Sade 2016	Cohort study of children born at the Soroka Medical Center to mothers belonging to the Clalit Health Maintenance Organization (HMO)	Southern Israel	1999-2008	Linkage between HMO and medical center databases

Part 2: Exposures, outcomes, and variables used for confounder control

Author Year	Prenatal Exposure	Outcome in Child	Variables Used for Confounder Control
Dehlink 2009	Medical Birth Register record of maternal use of H2RA, PPI, or other gastric acid suppressive	1995-2006 hospitalization for asthma and other allergic disease (i.e., atopic dermatitis, food allergy, unspecified allergic reaction/anaphylaxis, or allergic rhinitis or ≥ 2 prescriptions between July 2005 and December 2006 for an asthma medication, steroid ointment, epinephrine auto-injector, or antihistamine	Year of birth and maternal age, parity, smoking, and body mass index
Andersen 2012	Maternal prescriptions during pregnancy (30 days before LMP through delivery)	After birth, hospital, outpatient, or emergency-room visit for asthma or ≥ 2 prescriptions for β -agonist and inhaled glucocorticoid	Year of birth, county of residence, gender of child, gestational age, birth order, mode of delivery, mother's age at delivery, maternal smoking in pregnancy, maternal use of systemic antibiotics during pregnancy, and maternal history of asthma recorded at any time prior to delivery
Hak 2013	Maternal prescription during pregnancy (335-day period before delivery)	First asthma diagnosis before age 15 years, if followed within 12 months by ≥ 3 prescriptions for drugs used to treat asthma	Gender, birth order, age of the mother at birth, and number of prenatal general practitioner visits
Källén 2013	Medical Birth Register record of maternal drug use during second or third pregnancy trimester	≥ 5 prescriptions for asthma after 2 years of age	Year of birth and maternal age, parity, smoking, and body mass index
Mulder 2013	Maternal prescriptions during pregnancy (273 days before delivery through day of delivery)	After birth, ≥ 2 prescriptions in 6 month period for drugs used to treat asthma (ATC R03)	age of the mother at delivery (Study 2)
Mulder 2014	Maternal prescriptions during pregnancy (273 days before delivery through day of delivery)	After birth, ≥ 2 prescriptions in 12 month period with atopic dermatitis defined steroid or calcineurin ointment, asthma by inhaled corticosteroid, and allergic rhinitis by nasal steroids	Year of birth, sex of child, use of acid-suppressive drugs by child before index date, age of mother at delivery, maternal use of systemic antibiotics during pregnancy, and allergic disease in the mother

Author Year	Prenatal Exposure	Outcome in Child	Variables Used for Confounder Control
Cea Soriano 2016	≥1 prescription for H2RA or PPI between LMP and delivery	Electronic screen for asthma-related Read codes, confirmed by manual review of electronic medical records	sex of child, number of maternal PCP visits and referrals during year before LMP through end of pregnancy, maternal comorbidities (asthma, allergies, GERD, and peptic ulcer), and maternal use of NSAIDs, antacids, antibiotics, and antihistamines during pregnancy
Yitshak-Sade 2016	Maternal prescriptions 2 months before conception through end of pregnancy	After 2 nd birthday, (1) hospital episode under diagnostic code for asthma or wheezing, in absence of codes for cystic fibrosis, acute bronchiolitis, bronchitis, heart failure, chronic airway obstruction, pulmonary diseases, gastroesophageal reflux, and heart defects or (2) prescriptions for asthma medications, as defined by complex algorithm	Birth year, maternal factors (age, allergy, asthma, and infertility treatment), prenatal exposures (antibiotics, nonsteroidal anti-inflammatory drugs, metoclopramide, and insulin), lack of prenatal care, factors determined at birth (sex, preterm birth, cesarean section delivery, and low birth weight), and childhood exposure to H2RA or PPI before 2 years of age

ABBREVIATIONS: GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; LMP, last menstrual period; NSAIDs, non-steroidal anti-inflammatory drugs; PCP, primary care physician; PPI, proton pump inhibitor

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/s/

JOEL L WEISSFELD
03/06/2017

KIRA N LEISHEAR
03/06/2017

LOCKWOOD G TAYLOR
03/06/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 3, 2017
Requesting Office or Division:	Division of Gastroenterology & Inborn Error Products (DGIEP)
Application Type and Number:	NDA 209463
Product Name and Strength:	Pantoprazole Sodium for injection, 40 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Exela Pharma Sciences
Submission Date:	June 7, 2017
OSE RCM #:	2016-1389
DMEPA Primary Reviewer:	Matthew Barlow, RN, BSN
DMEPA (Acting) Associate Director:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review is in response to a request from DGIEP to evaluate the proposed labels and labeling submitted by the applicant under NDA 209463, from a medication errors perspective. The applicant submitted proposed container labels, carton labeling, and prescribing information (PI) on June 7, 2016 as a 505(b)(2) application to the Reference Listed Drug (RLD) Protonix I.V. (NDA 209088).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant submitted the proposed labels and labeling, under NDA 209463, as a 505(b)(2) citing NDA 209088, Protonix I.V., as the reference listed drug (RLD). The proposed drug differs from the reference product with respect to the inactive ingredients that are present in the RLD. Specifically, the RLD contains Edetate Disodium, while the proposed product does not contain this inactive ingredient. However, the products share the same strength and dose, and are both available as a 40 mg per vial lyophilized powder. DMEPA performed a risk assessment of the proposed label for areas of vulnerability that may lead to medication errors. We note areas of the proposed container and carton labels that can be revised to improve clarity and understanding. Specifically, we note the use of the abbreviation 'I.V.' on the labels and labeling to express the route of administration, which can be misinterpreted. The established name can be revised to increase the prominence of this information, by increasing the font size and using bold font, on the proposed carton label. Additionally, we note that the statement "Single-dose vial –Discard unused portion" can be added to the labels and labeling to ensure that the product is safely used and handled. We provide recommendations for the applicant in Section 4 to address these identified deficiencies.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling can be improved to clarify information and promote the safe and effective use of the product. We provide recommendations for the applicant in section 4.2 to address these issues:

4.1 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES

We recommend the following be implemented prior to approval of this NDA:

A. Container Label and Carton Labeling

1. We recommend revising the route of administration statement “For I.V. infusion only” to “For Intravenous Infusion Only.” Furthermore, revise any other abbreviation “I.V.” to “Intravenous,” on the container label and carton labeling as we recommend avoiding the use of abbreviations to prevent misinterpretation.^a
2. We recommend adding the statement “Single-dose vial –Discard unused portion” to the PDP, below the route of administration statement to provide information on the appropriate use of this product.
3. As currently presented, the NDC number is denoted by a placeholder; therefore, please revise the proposed labels and labeling to include the actual number.

B. Container Label

1. As currently presented, the barcode is denoted by a placeholder; therefore, please revise the proposed carton labeling to include the actual barcode.

C. Carton Label

1. We recommend increasing the prominence of the established name (e.g. increasing font size and bold font), as this should be the most prominent information on the Principal Display Panel (PDP)^b.

^a ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2017 FEB 02]. Available from: <https://www.ismp.org/tools/errorproneabbreviations.pdf>.

^b Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pantoprazole Sodium that Exela submitted on June 7, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Pantoprazole and the Listed Drug		
Product Name	Pantoprazole Sodium	Protonix I.V.
Initial Approval Date	N/A	March 22, 2001
Active Ingredient	Pantoprazole Sodium	Pantoprazole Sodium
Indication	Pantoprazole Sodium for Injection is indicated for short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE). Pantoprazole Sodium for Injection is indicated for the treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome in adults.	PROTONIX I.V. for Injection is indicated for short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis. PROTONIX I.V. for Injection is indicated for the treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome in adults.
Route of Administration	Intravenous	Intravenous
Dosage Form	Lyophilized Powder	Lyophilized Powder
Strength	40 mg/Vial	40 mg/Vial
Dose and Frequency	Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis <u>Recommended Dosage</u> The recommended adult dosage is 40 mg given once daily by intravenous infusion for 7 to 10 days. Pathological Hypersecretion Including Zollinger-Ellison Syndrome <u>Recommended Dosage</u> The recommended adult dosage is	Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis <u>Recommended Dosage</u> The recommended adult dose is 40 mg pantoprazole given once daily by intravenous infusion for 7 to 10 days. Pathological Hypersecretion Including Zollinger-Ellison Syndrome <u>Recommended Dosage</u>

	80 mg intravenously every 12 hours.	The recommended adult dosage is 80 mg intravenously every 12 hours.
How Supplied	Pantoprazole Sodium for Injection is supplied as a freeze-dried powder containing 40 mg of pantoprazole per vial. Pantoprazole Sodium for Injection is available as follows: • NDC xxxx-xxx-xx – Single vial containing Pantoprazole Sodium for Injection (contains 40 mg of pantoprazole). • NDC xxxx-xxx-xx – Package of 10. Each vial (NDC xxxx-xxxx-xx) contains Pantoprazole Sodium for Injection (each vial containing 40 mg pantoprazole).	PROTONIX I.V. (pantoprazole sodium) for Injection is supplied as a freeze-dried powder containing 40 mg of pantoprazole per vial. PROTONIX I.V. for Injection is available as follows: • NDC 0008-0923-51 – Single vial containing PROTONIX I.V. for Injection (contains 40 mg of pantoprazole). • NDC 0008-0923-55 – Package of 10. Each vial contains PROTONIX I.V. for Injection (each vial containing 40 mg pantoprazole). • NDC 0008-0923-60 – Package of 25. Each vial contains PROTONIX I.V. for Injection (each vial containing 40 mg pantoprazole).
Storage	Store Pantoprazole Sodium for Injection vials at 20° – 25°C (68° – 77°F); excursions permitted to 15° – 30°C (59° – 86°F) [see USP Controlled Room Temperature]. Protect from light. The reconstituted product should not be frozen.	Store PROTONIX I.V. for Injection vials at 20° – 25°C (68° – 77°F); excursions permitted to 15° – 30°C (59° – 86°F) [see USP Controlled Room Temperature]. Protect from light. The reconstituted product should not be frozen.

APPENDIX B. PREVIOUS DMEPA REVIEWS—N/A

APPENDIX C. HUMAN FACTORS STUDY—N/A

APPENDIX D. ISMP NEWSLETTERS—N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A

APPENDIX F.—N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Pantoprazole Sodium labels and labeling submitted by Exela on June 7, 2016.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

(b) (4)



B. Carton Label

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW J BARLOW
03/03/2017

MISHALE P MISTRY
03/03/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209463 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Established/Proper Name: Pantoprazole sodium Dosage Form: IV infusion Strengths: 40 mg vial		
Applicant: Elexla Pharma Sciences Agent for Applicant (if applicable):		
Date of Application: 2 Jun 2016 Date of Receipt: 7 Jun 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: 7 Apr 2017		Action Goal Date (if different):
Filing Date: 6 Aug 2016		Date of Filing Meeting: ~ 22 Jul 2016
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): <i>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 in adults.</i>		
Type of Original NDA, AND (if applicable): Type of NDA Supplement: <i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA	☐ 351(a) ☐ 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
<i>The application will be a priority review if:</i> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): PIND 118432

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic</i>	☒	☐		

<i>archive.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	☒	☐	☐	CDR contacted to update application coding on 20 Jun 2016
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☐	☒		Checked 10 Jun 2016
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	☐	☐		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		Sponsor contacted to provide signed form on 20 Jun 2016
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:	☒	☐		

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒																		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☒		Per 7/10/2016 email from M. Shimer: The presence of NaOH in the proposed formulation precludes the Exela product (b) (4) [REDACTED] I also believe that the formulation proposed by Exela will be implicated by the relisting determination for the original formulation of Protonix I.V. since Exela is not proposing the use of the chelating agent edetate disodium.																
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	☐	☒		Per 7/10/2016 email from M. Shimer: The presence of NaOH in the proposed formulation precludes the Exela product from submission as an (b) (4) [REDACTED] I also believe that the formulation proposed by Exela will be implicated by the relisting determination for the original formulation of Protonix I.V. since Exela is not proposing the use of the chelating agent edetate disodium.																
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													☐	☒		Checked 10 Jun 2016; checked under discontinued products on 20 Jun 2016 and No matching records found.
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																				

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒		Checked 10 Jun 2016
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes , # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD

	☒ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no , explain.	☐	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	☐	☐	☒	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	Sponsor contacted to provide on 20 Jun 2016

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	☐	☒		Not required, as no clinical data was provided.
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	☒	☐		CDR contacted on 20 Jun 2016 to update record in DARRTS
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment

For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> For non-NMEs: <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☐	☒		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☒	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	☐	☒		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☐	☒	☐	

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☒	☐	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	☐	☒		Sponsor contacted to provide on 20 Jun 2016
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	☐	☒	☐	Consult request submitted to DPMH on 20 Jun 2016; filing issue???
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☐	☒	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	☐	☒	☐	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☐	☒	☐	Consult request submitted to OPDP on 20 Jun 2016

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	☒	☐	☐	Consult request submitted to DRISK on 20 Jun 2016
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	Consult request submitted to DMEPA on 20 Jun 2016
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/package sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☐	☒	☐	I don't think any additional consults warranted (outside of the consults typically issued for a NDA review)
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	☐	☒		
Any Special Protocol Assessments (SPAs)? Date(s):	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE:

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:		
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)			
Division Director/Deputy			
Office Director/Deputy			
Clinical	Reviewer:		
	TL:		
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:		
	TL:		
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:		
	TL:		

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Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:		
	RBPM:		
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL 505 b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):		☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☐ YES ☐ NO	
Electronic Submission comments List comments:	☐ Not Applicable ☐ No comments	

CLINICAL Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☐ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☐ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☐ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☐ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☐ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☐ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
<u>APPLICATIONS IN THE PROGRAM (PDUFA V)</u> <u>(NME NDAs/Original BLAs)</u> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☐ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRA completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAWRENCE W ALLAN
06/20/2016