CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207963Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 207963	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Not applicable Established/Proper Name: palonosetron hydrochloride Dosage Form: injection Strengths: 0.25 mg/2 mL		
Applicant: Exela Pharma Sciences, LLC		
Date of Receipt: August 8, 2014. Complete Response (CR) issued June 15, 2015. Response to CR received September 22, 2015. Tentative Approval issued March 22, 2016. Request for final approval received June 22, 2016.		
PDUFA Goal Date: August 22, 2016	Action Goal Date (if different):	
RPM: Mary Chung		
Proposed Indication(s) for ADULTS: 1. Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses 2. Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses		

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 021372 Aloxi (palonosetron hydrochloride) injection	Highlights of Prescribing Information (all sections) Full Prescribing Information – all sections except 11 Description and 16 How Supplied/Storage and Handling Patient Labeling Patient Labeling – all sections except "What are the ingredients in Palonosetron Hydrochloride Injection?"

*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 literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The proposed product differs from the listed product in that the proposed product does not contain any buffer, mannitol, and disodium edetate (EDTA).

Although the criteria for a biowaiver under 21 CFR 320.22(b)(1) is not fully met, based on 21 CFR 320.24(b)(6), the FDA can rely on any other approach deemed adequate by FDA to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products. Specifically for this proposed product, the absence of buffer, mannitol, and EDTA in the formulation of the proposed drug product is not expected to impact the bioavailability of palonosetron following intravenous (IV) administration. The rationale is as follows:

- EDTA is used in the listed drug product (b) (4) Therefore, the bioavailability of

[1]For 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

the proposed product is not expected to change during the labeled expiration dating period.

- The pH of the proposed product (measured pH (b) (4)) is different than that of the listed product (measured pH 5.0). However, proposed product's pH range encompasses the normal pH range of blood ((b) (4)). Based on the buffer capacity of blood and total volume of administration, this is considered acceptable. Therefore, the difference in pH between the proposed and listed drug products is not expected to impact pharmacokinetics of the proposed product.
- Although mannitol is an osmotic diuretic that can affect kidney function, absence of small amount of mannitol ((b) (4) mg) is not expected to affect palonosetron renal clearance.

In conclusion, as consistent with 21 CFR 320.24(b)(6), there is adequate information supporting the relative bioavailability of Exela's proposed drug product to the listed drug establishing the scientific bridge. Thus, additional in vivo bioequivalence (BE) bridging study is not needed.

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).*

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

YES ☐ NO ☐

[1]For 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)
Aloxi (palonosetron hydrochloride) Injection	021372	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").

Exela's proposed formulation contains the same active (b) (4) ingredients as the reference product, except for (b) (4) Exela's formulation contains no mannitol (b) (4) disodium edetate (b) (4) or citrate (b) (4) The active ingredient concentration of Exela's product is 0.125 mg/mL (dosage strength: 0.025mg/2mL single-dose vial), compared to the reference Aloxi's which is 0.05 mg/mL (dosage strength: 0.25mg/5 mL and 0.075 mg/1.5 mL single-dose vial).

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.*

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):
NDA 021372, Aloxi injection
NDA 203050, Palonosetron Hydrochloride Injection
There are 3 generic pharmaceutical alternative products listed in the Orange Book (ANDA 202521, ANDA 90713, ANDA 201533).

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):

All patents under NDA 021372 Aloxi (palonosetron hydrochloride) injection

5202333
7947724
7947725
7960424
8518981
8598218
8598219
8729094

Below are patents listed since the June 22, 2015 Complete Response

9066980
9125905
9173942

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): 5202333 Expiry date(s): October 13, 2015

☒ 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):
7947724, 7947725, 7960424, 8518981, 8598218, 8598219, 8729094, 9066980, 9125905, 9173942

(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):

Regarding patents 5202333, 7947724, 7947725, 7960424, 8518981, 8598218, 8598219, 8729094

Dates: October 17, 2014, October 20, 2014
Note: The NDA and patent owners [Helsinn Healthcare SA (Switzerland) and Roche Palo Alto LLC] received notifications on the dates listed above. (Exela also informed Troutman Sanders LLP, which sponsor indicates is the patent owner or patent owner representative according to the USPTO PAIR website). Exela provided the USPS Track/Confirm web print outs to confirm these dates. Helsinn Healthcare SA and Roche are listed as the patent owners on the patent forms. Lawsuit has been jointly filed by Helsinn and Roche for patents 8518981, 8598218.

Regarding patents 9066980, 9125905, 9173942

Dates: August 27, 2015, August 28, 2015, October 13, 2015, October 14, 2015, October 15, 2015, October 19, 2015, November 16, 2015

Note:
The NDA and patent owners [Helsinn Healthcare SA and Roche Palo Alto LLC] received notifications on the dates listed above. (Exela also informed Troutman Sanders LLP, which sponsor indicates is the patent owner or patent owner representative according to the USPTO PAIR website). Exela provided the USPS Track/Confirm web print outs to confirm these dates. Helsinn Healthcare SA and Roche are listed as the patent owners on the patent forms. Lawsuit has been jointly filed by Helsinn and Roche for patent 9125905.

(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

Lawsuit filed on December 1, 2014 for patent 8518981 and 8598218. On May 9, 2016, this lawsuit was dismissed.

Lawsuit filed on October 8, 2015 for patent 9125905. On May 10, 2016, the lawsuit against the applicant concerning patent 9125905 was dismissed.

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/s/

MARY H CHUNG
08/22/2016

ADDENDUM

TO 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)

Date of This Memorandum:	March 21, 2016
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 207963
Product Name and Strength:	Palonosetron Hydrochloride injection, for intravenous use 0.25 mg/2 mL (0.125 mg/mL)
Submission Date:	September 22, 2015
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
OSE RCM #:	2014-1984-2
DMEPA Team Leader (Acting):	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS

1 PURPOSE OF ADDENDUM

This review further evaluates the risk of medication errors involving this product, as an addendum to a previous label and labeling review.[1]

2 DISCUSSION

On August 7, 2014, Exela Pharma Sciences, LLC ("EPS") submitted a 505b(2) NDA to the Reference Listed Drug (RLD), Aloxi (NDA 021372). In the original submission, the Applicant proposed a new concentration of palonosetron, 0.25 mg/2 mL (0.125 mg/mL) in a vial, compared to the currently marketed palonosetron (0.25 mg/5 mL [0.05 mg/mL in a vial] and 0.075 mg/1.5 mL [0.05 mg/mL in a vial]). EPS initially pursued the chemotherapy-induced nausea and vomiting (CINV) indication (dose of 0.25 mg intravenously administered over 30

[1] Abraham S. Label and Labeling Review for Palonosetron (NDA 207963). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Jan 15. 16 p. OSE RCM No.: 2014-1984.

seconds) (b) (4) in adults. On June 15, 2016, the Agency issued the Applicant a Complete Response to their submission, which included a number of deficiencies and among them a deficiency that EPS has not provided adequate information to establish that the proposed concentration would not increase the potential for dosing errors with palonosetron. FDA suggested in the CR letter that to satisfy this deficiency, the Applicant should conduct a Human Factors study to characterize the risks of confusion and dosing errors between the currently marketed concentration of palonosetron (0.05 mg/mL) and the proposed concentration and to demonstrate that the proposed strategies to address the identified risks mitigate the potential for errors.

On September 22, 2015, the Applicant resubmitted the 505b(2) NDA, providing a formal response to the Complete Response. In response to FDA's stated concern for dosing errors due to the difference in concentration between the proposed product and currently marketed product, the Applicant proposed labeling (b) (4) and the respective recommended dosing instruction mitigated any potential for dosing errors.

Currently, the Applicant is only pursuing the CINV adult indication and the labeling contains only the recommended dosing regimen specifically for CINV. As it relates to the risk of medication errors, CINV requires a single total dose of the total vial volume, or 0.25 mg, which is the entire content of EPS's 2 mL vial presentation and of Aloxi's 5 mL vial presentation.

(b) (4) On a similar note, DMEPA acknowledges that the proposed product might also be used off-label for the pediatric indication of chemotherapy-induced nausea and vomiting indication, which is a weight-based dosing regimen of 20 mcg/kg (maximum dose of 1.5 mg). The Applicant's response to the Complete Response by itself is not sufficient to address FDA's concerns with the concentration of this product having some potential for dosing errors.

However, in the course of our current review, we have further considered this issue and in order to address this risk of dosing errors, we provided recommendations to EPS that are intended to highlight the difference in the concentration of this product in labeling and reduce the likelihood of the aforementioned dosing errors. EPS has accepted and implemented our recommendations, which are reflected in the labeling submitted on March 14, 2016 and March 17, 2016. Our recommendations are consistent with those related to other drug products marketed in varying concentrations where there is sufficient data available for us to conclude that label and labeling measures have adequately minimized the risk of harmful dosing errors. Based on our current experience and understanding of medication errors related to confusion caused by the introduction of a new concentration of a drug substance, it is reasonable to conclude that employing similar strategies for this particular product will likewise reduce the risks of dosing errors if this EPS palonosetron product is used off-label to treat CINV in pediatric patients (b) (4) These risk reduction measures should reduce the likelihood for error in adult and pediatric patients treated with the proposed EPS palonosetron product. Importantly, based on the clinical reviewer's input, we note that the safety risks due to dosing errors that

may occur, although undesirable, could result in overdose, and that the overdoses we would expect to see may have minimal consequence from a clinical perspective as it would be unlikely to produce a serious adverse event.

3 CONCLUSION

Based on the above information, DMEPA concludes that the safety risk associated with dosing errors with the proposed higher concentration of palonosetron have minimal impact from a clinical perspective and that these risks of dosing errors is adequately managed in the currently proposed product's labels and labeling (submitted on March 14, 2016 and March 17, 2016), as recommended in the previously referenced review. We have no further recommendations at this time.

APPENDIX A. LABEL AND LABELING SUBMITTED ON MARCH 14, 2016 AND MARCH 17, 2016

Container Label (submitted March 17, 2016)

Carton Labeling (submitted March 14, 2016)

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

/s/

MISHALE P MISTRY
03/21/2016

LUBNA A MERCHANT
03/21/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric and Maternal Health Labeling Review

From:	Amy M. Taylor, MD, MHS Medical Officer Division of Pediatric and Maternal Health Miriam Dinatale, D.O., Medical Officer, Maternal Health Division of Pediatric and Maternal Health
Through:	Hari Cheryl Sachs, MD Team Leader Division of Pediatric and Maternal Health Tamara Johnson, MD, MS, Team Leader, Maternal Health Division of Pediatric and Maternal Health John J. Alexander, MD, MPH Acting Deputy Director Division of Pediatric and Maternal Health
NDA Number:	207-963
Sponsor:	Exela Pharma Sciences
Drug:	Palonosetron Injection
Dosage form and route of administration:	injection for intravenous use
Proposed indications:	Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses

Consult request: The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests assistance from the Division of Pediatric and Maternal Health (DPMH) as they review this 505(b)(2) NDA, including labeling.

Background

The sponsor originally submitted this 505(b)(2) NDA relying on the findings of safety and efficacy of Aloxi® (palonosetron HCl) NDA 21-372 on August 7, 2014. The application received a Complete Response on June 15, 2015. The sponsor submitted a resubmission on September 22, 2015. The application does not trigger PREA.

The innovator, Aloxi®, received pediatric exclusivity on April 10, 2014 and was approved for prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy in pediatric patients aged 1 month to less than 17 years on May 27, 2014. Of note, an assessment of Aloxi® f (b) (4) Thus, Aloxi has the following indications:

Aloxi® is a serotonin-3 (5-HT3) receptor antagonist indicated in adults for:

- Moderately emetogenic cancer chemotherapy --prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy --prevention of acute nausea and vomiting associated with initial and repeat courses
- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated

Aloxi® is indicated in pediatric patients aged 1 month to less than 17 years for:

- Prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy

Hypotonicity of the product

This product has a tonicity of approximately 0 mOSM/kg. Safety concerns including injection site pain and hemolysis were raised because of the hypotonicity of the formulation. The sponsor conducted a local irritation study which confirmed that this product does not present a safety concern related to local irritation. The sponsor also conducted an *in vitro* hemolysis study which does not suggest that the hypotonic solution of the 2 mL adult dose will result in clinically relevant hemolysis. The highest concentration tested was a 1:10 dilution which did not demonstrate significant hemolysis.

Concern was raised that the hypotonicity of the formulation may cause a safety concern in pediatric patients if this product is used off-label in pediatric patients. However, calculations of potential dosing based on the recommended dosing in the Aloxi labeling show that the dilution in the average blood volume for weight was approximately 1:500. The following chart was developed by Dr. Aisha Johnson, a clinical reviewer in DGIEP. See Dr. Johnson's review for additional information.

Pediatric Dose/Volume Estimates and Calculated TBV Dilution[1]

Age	Weight*	Dose‡ (20 mcg/kg)	Drug Volume§ (0.125 mg/mL)	Average Total Blood Volume# (mL)	Dilution†
1 month	4.4 kg	0.088 mg	0.7 mL	350	1:500
6 months	6.4 kg	0.13 mg	1 mL	500	1:500
9 months	7.4 kg	0.14 mg	1.1 mL	600	1:545
6 years	16 kg	0.32 mg	2.6 mL	1120	1:430
10 years	26 kg	0. 52 mg	4.2 mL	1820	1:433
16 years	50 kg	1.0 mg	8.0 mL	3500	1:437
		MAX DOSE 1.5 mg	**MAX VOLUME** 12 mL		

Reviewer's Table.
*Weight based on CDC growth charts, 5th percentile average of boys and girls
#Total Blood Volume estimated using approximation to Nadler's equation (80 mL/kg until 1 year, then 70 mL/kg)
‡Dose (in mg) calculated as Weight X .020 mg/kg
§Drug volume (in mL) calculated as follows: Dose (in mg) / 0.125 mg/mL

1 http://www.cdc.gov/growthcharts/data/who/grchrt_boys_24lw_100611.pdf and http://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf

Reviewer comment: The 1:500 dilution compared to the 1:10 dilution in the in vitro *study provides reassurance that significant hemolysis should not occur if this product is administered to pediatric patients.*

Discussion and Recommendations

The indication sections of the Highlights section appropriately expresses that the indication is approved in adults only for this product. The indication section in the Full Prescribing Information should express that the indication is approved in adults only for this product as well.

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. 21 CFR 201.57(c)(9)(iv) describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population and allows an alternative statement to be included if the required statement is not appropriate.

Pregnancy and Lactation Labeling Recommendations

In April 2015 and January 2016, DPMH conducted a review of published literature regarding palonosetron and pregnancy, lactation and females and males of reproductive potential, and provided labeling recommendations for this application to comply with the Pregnancy and Lactation Labeling Rule (PLLR). The reader is referred to the DPMH reviews by M. Dinatale, D.O., for further details.[1,2] Previous labeling recommendations,

[1] DPMH review of palonosetron Hydrochloride (NDA 207963). Miriam Dinatale, DO. April 29, 2015. DARRTS Reference ID 3741833

that were not applied due to issuance of the Complete Response, are now being implemented in the current palonosetron labeling. No new labeling recommendations are provided at this time.

Sponsor Proposed Pediatric Labeling and DPMH Recommended Labeling

1 INDICATIONS AND USAGE

1.1 Chemotherapy-Induced Nausea and Vomiting

Palonosetron Injection is indicated in adults for:

- Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses

- Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses

8.4 Pediatric Use

(b) (4)

This product has not been approved for use in pediatric patients for prevention of chemotherapy-induced nausea and vomiting.

Rationale

Safety and effectiveness of the Aloxi® formulation of palonosetron has been demonstrated in pediatric patients aged 1 month to less than 17 years for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy. Information on pediatric dosing, safety, pharmacokinetics, and a description of the pediatric studies supporting pediatric use is protected by the exclusivity awarded to the innovator Aloxi®. Therefore, this information cannot be included in labeling for this 505(b)(2) product. Including a statement that safety and effectiveness have not been established for pediatric patients for the CINV indication would not be a true statement. Safety and effectiveness have been established for pediatric CINV in Aloxi® (b) (4) tating that "this product has not been approved for pediatric use" is a true statement and is an alternative statement as allowed under the regulations. DPMH recommends using the more general indication of "chemotherapy-induced nausea and vomiting" in order to avoid the possibility of including protected information in the labeling. (b) (4)

[2] DPMH review of palonosetron Hydrochloride (NDA 203050). Miriam Dinatale, DO. January 25, 2016. DARRTS Reference ID 3875380

Additional comments:

The hypotonicity of this product does not represent a safety concern if the product is administered off-label in pediatric patients.

These recommendations were communicated to DGIEP during labeling meetings. Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations.

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/s/

AMY M TAYLOR
03/02/2016

MIRIAM C DINATALE
03/02/2016

HARI C SACHS
03/02/2016
I agree with these recommendations.

TAMARA N JOHNSON
03/02/2016

JOHN J ALEXANDER
03/02/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 23, 2016
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	PALONOSETRON injection
Dosage Form and Route:	for intravenous use
Application Type/Number:	NDA 207963
Applicant:	Exela Pharma Sciences, LLC

1 INTRODUCTION

On September 15, 2015, Exela Pharma Sciences, LLC re-submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 207963 for PALONOSETRON injection for intravenous use. The Division of Gastroenterology and Inborn Errors Products (DGIEP) considers the Applicant's submission to be a complete, class 2 response to the Agency's Complete Response Letter issued on June 15, 2015. The Reference Listed Drug (RLD) is ALOXI (palonosetron HCl) Injection for Intravenous Use NDA 021372. The proposed indication for PALONOSETRON injection for intravenous use is for the treatment of:

- Moderately emetogenic cancer chemotherapy-prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy-prevention of acute nausea and vomiting associated with initial and repeat courses

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Gastroenterology and Inborn Error Products (DGIEP) on November 4, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PALONOSETRON injection for intravenous use.

2 MATERIAL REVIEWED

- Draft PALONOSETRON injection for intravenous use PPI submitted on September 15, 2015 and received by DMPP and OPDP on February 11, 2016.
- Draft PALONOSETRON injection for intravenous use Prescribing Information (PI) submitted on September 15, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 23, 2016.
- Approved ALOXI (palonosetron HCl) Injection for Intravenous Use comparator labeling dated September 18, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
02/23/2016

MEETA N PATEL
02/23/2016

SHAWNA L HUTCHINS
02/23/2016

LASHAWN M GRIFFITHS
02/23/2016

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

Memorandum

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

Date: February 17, 2016

To: Mary Chung
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 207963
OPDP Comments for draft palonosetron injection for intravenous use

OPDP has reviewed the proposed draft PI, and carton/container labeling for palonosetron injection for intravenous use. We have reviewed the draft PI, emailed to us on February 11, 2016, and have two additional comments. We have reviewed the draft carton/container labeling, retrieved on February 17, 2016, and have no additional comments. Comments on the draft PPI will be sent under separate cover as a joint review with DMPP.

Thank you for the opportunity to comment on the proposed PI and carton/container labeling.

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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/s/

MEETA N PATEL
02/17/2016

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:	January 15, 2016
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 207963
Product Name and Strength:	Palonosetron Hydrochloride Injection 0.25 mg/2 mL
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
Submission Date:	September 22, 2015
OSE RCM #:	2014-1984
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, M.S., Pharm.D.

1 REASON FOR REVIEW

This review evaluates the labels and labeling for Palonosetron injection, NDA 207963, submitted on September 22, 2015. The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that DMEPA review the proposed prescribing information, carton labeling, and container labels for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

On August 7, 2014, Exela Pharma Sciences, LLC submitted a 505 b(2) NDA to provide a new strength (0.125 mg/mL) of palonosetron from the Reference Listed Drug, Aloxi (NDA 021372). In the Complete Response letter dated June 15, 2015, DMEPA requested that the Applicant conduct a human factors study to characterize the risks of confusion and dosing between the currently marketed concentration of Palonosetron (0.05 mg/mL) and the proposed concentration (0.125 mg/mL) to establish that the proposed concentration would not increase the potential for dosing errors. (b) (4)

3 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
FDA Adverse Event Reporting System (FAERS)*	E
Other	F
Labels and Labeling	G

N/A=not applicable for this review

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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Exela Pharma Sciences, LLC submitted a 505 (b)(2) NDA to obtain marketing approval of Palonosetron Hydrochloride injection 0.125 mg/mL. The reference listed drug (RLD) for this product is Aloxi (Palonosetron Hydrochloride Injection), which is currently marketed in 0.075 mg/1.5 mL (0.05 mg/mL) and 0.25 mg/ 5 mL (0.05 mg/mL). Exela proposes a higher strength formulation of 0.25 mg/2 mL (0.125 mg/mL). We note that the Applicant is proposing a new strength for this product while the active ingredient, dosage form, and route of administration are the same as the reference listed product. Aloxi is currently approved for chemotherapy-induced nausea and vomiting (CINV) and post-operative nausea and vomiting (PONV). The adult dose for CINV is 0.25 mg as a single dose (delivery of entire 5-mL vial) and a pediatric dose of 20 mcg/kg (max 1.5 mg) as a single dose. The dose for PONV is 0.075 mg as a single intravenous dose (delivery of entire 1.5-mL vial). Exela is proposing an indication for CINV at a single dose of 0.25 mg. Because the strength of the proposed palonosetron is higher than what is currently approved for Aloxi, we were concerned about the risk of dosing errors.

We have considered the risks of dosing errors with this new strength and compared the carton labeling and container labels of the proposed formulation and the RLD, Aloxi. We identified areas in the container label and carton labeling that can be improved to increase the readability and prominence of important information to address the concern for dosing errors due to the potential confusion with Aloxi, and to promote the safe use of the product. We provide the recommendations in Section 4 to address the deficiencies.

5 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES, LLC

Based on this review, we recommend the following be implemented prior to approval of this NDA:

Carton and container labels:

1. Add a cautionary statement (b) (4) to the principal display panel that this product is higher in concentration than the reference listed drug product to avoid dosing errors. For example, (b) (4) ."
2. To mitigate the risk of confusion with the reference listed drug's strength and subsequent dosing errors, we recommend revising the statement of (b) (4)

(b) (4)

(b) (4)

3. Increase the prominence of the established name by increasing the font size.

4. As currently presented, the NDC number is located (b) (4) the carton labeling. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling, in accordance with 21 CFR 207.35(3)(i). Relocate the NDC number from the side panel to the top third of the principal display panel.

5. As currently presented, there are (b) (4) Rx only statements on the side panel. Please move one statement to the bottom right corner of the principal display pane (b) (4)

6. Add a usual dosage statement to the side panel. For example, "Usual dose: See prescribing information".

7. Remove the trailing zero from the strength presentation (0.25 mg/2 mL) to avoid misinterpretation of the product strength.

8. Delete the (b) (4) statement since the proposed adult dosage for this formulation is the entire vial (0.25 mg).

9. Revise the (b) (4) statement to "2 mL single dose sterile vial" since the term "single dose" accurately describes the correct usage of this product in single patient as a single injection[1].

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Palonosetron Hydrochloride that Exela Pharma Sciences, LLC submitted on September 22, 2015.

Table 2. Product Information Comparison for Aloxi and Palonosetron Hydrochloride Intravenous Injection 0.25 mg /2 mL

	Aloxi (Palonosetron) (NDA 021372)	**Palonosetron (NDA 207963)**
Initial Approval Date	July 25, 2003	N/A
Active Ingredient	Palonosetron Hydrochloride	Palonosetron Hydrochloride
Indication	Palonosetron Injection is a serotonin subtype 3 (5-HT3) receptor antagonist indicated in adults for: Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses. Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses. Prevention of postoperative nausea and vomiting (PONV) for upto 24 hours following surgery. Pediatrics: 1 month to 17 years for prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy.	Palonosetron Injection is a serotonin subtype 3 (5-HT3) receptor antagonist indicated in adults for: Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses. Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses.
Route of Administration	Intravenous	Intravenous
Dosage Form	Injection	Injection

Strength	0.25 mg/5 mL 0.075 mg/1.5 mL	0.25 mg /2 mL
Dose and Frequency	Chemotherapy-Induced Nausea and Vomiting: Adults: 0.25 mg as a single intravenous dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy. Pediatrics: 20 mcg/kg (max 1.5 mg) as a single dose administered over 15 minutes 30 minutes before the start of chemotherapy. Postoperative Nausea and Vomiting: 0.075 mg as a single intravenous dose administered over 10 seconds immediately before the induction of anesthesia.	Chemotherapy-Induced Nausea and Vomiting: 0.25 mg as a single intravenous dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy.
How Supplied	0.25 mg/5 mL-single use vial individually packaged in a carton. 0.075 mg/1.5 mL –single use vial package in a carton containing 5 vials.	Single (b) (4) vial individually packaged in a single carton.
Storage	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F).	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F).

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On December 28, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Palonosetron

D.2 Results

Our search identified one case, but was excluded since it was not relevant for this review.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on December 28, 2015, using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]

Table 3: FAERS Search Strategy	
Date Range	**January 1, 2014 to December 1, 2015**
Product	**Aloxi** (Product name) **Palonosetron** [active ingredient]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

E.2. Results

Our search did not identify any medication error cases that were relevant for this review and could be addressed by labels and labeling.

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[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

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/s/

SHERLY ABRAHAM
01/15/2016

MISHALE P MISTRY
01/19/2016

LUBNA A MERCHANT
01/19/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

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

Through: Lynne P. Yao, MD OND Acting Director
Division of Pediatric and Maternal Health

NDA Number: 207963

Sponsor: Exela Pharma Sciences

Drug: Palonosetron HCl (0.25 mg (free base) per 2 mL, supplied as 0.28 mg palonosetron hydrochloride)

Dosage form and route of administration: injection for intravenous use

Proposed indications: Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses

Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses

(b) (4)

Consult request: The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests assistance from the Division of Pediatric and Maternal Health (DPMH) as they review this 505(b)(2) NDA, including labeling.

Background

The sponsor submitted this 505(b)(2) NDA relying on the findings of safety and efficacy of Aloxi® (palonosetron HCl) NDA 21-372. The application does not qualify for the ANDA pathway for marketing approval because the product has a different concentration than the RLD.

The innovator, Aloxi®, received pediatric exclusivity on April 10, 2014 and was approved for prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy in pediatric patients aged 1 month to less than 17 years. (b) (4)

Aloxi® has the following indications:

Aloxi® is a serotonin-3 (5-HT3) receptor antagonist indicated in adults for:

- Moderately emetogenic cancer chemotherapy --prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy --prevention of acute nausea and vomiting associated with initial and repeat courses
- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated

Aloxi® is indicated in pediatric patients aged 1 month to less than 17 years for:

- Prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy

Sponsor's proposed labeling

(b) (4)

(b) (4)

Sponsor's request for a waiver

The sponsor requested a waiver of pediatric studies under PREA as part of the application stating that none of the (b) (4) "triggers" for PREA apply.

(b) (4)

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/s/

AMY M TAYLOR
06/10/2015

LINDA L LEWIS
06/11/2015
Signing as Acting Deputy Director, DPMH, on behalf of L. Yao, Acting Director, DPMH

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 207963

Application Type: New NDA

Name of Drug/Dosage Form: Palonosetron Hydrochloride Injection

Applicant: EXELA PHARMACEUTICAL SCIENCES LLC

Receipt Date: August 8, 2014

Goal Date: June 15, 2015

1. Regulatory History and Applicant's Main Proposals

The purpose of this submission is to submit for approval of the proposed drug product, Palonosetron Hydrochloride Injection, 0.125 mg/mL (0.25 (b) (4) mg/ 2 mL), a parenteral preparation. In accordance with 314.54(a)(1)(iii) and under Section 505(b)(2), we identify ALOXI® (Palonosetron Hydrochloride Injection), Helsinn Health care SA, as the previously approved drug under NDA No. N021372 for which FDA has made a finding of safety and effectiveness. Exela's proposed drug product has the same active ingredient, dosage form, route of administration, and indications as ALOXI® (Palonosetron Hydrochloride Injection). However, Exela's drug product differs from Helsinn Health care SA's listed drug product with respect to the active ingredient concentration and excipients used along with the active ingredient. The active ingredient concentration of the Helsinn Health care SA's listed drug product ALOXI® is 0.25 mg/5 mL or 0.075 mg/1.5 mL, whereas Exela's formulation contains active ingredient concentration as 0.125 mg/mL. Palonosetron hydrochloride Injection is being submitted for the indication of nausea and vomiting after/during moderately and highly emetogenic cancer chemotherapy treatments. (b) (4)

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required

Selected Requirements of Prescribing Information

• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

N/A 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

N/A 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *Subsections are bolded*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JAMES B CARR
06/09/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: April 28, 2015 **Date Consulted:** September 24, 2014

From: Miriam Dinatale, D.O., Medical Officer
Division of Pediatric and Maternal Health

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

Lynne P. Yao, MD, Acting Division Director
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Palonosetron Hydrochloride (HCl) Injection

NDA: 207963

Applicant: Exela Pharma Sciences

Subject: Pregnancy and Lactation labeling

Proposed Indication: Prevention of nausea and vomiting after/during moderately and highly emetogenic cancer and chemotherapy treatments (b) (4)

Materials Reviewed:

- DPMH consult request dated September 24, 2014, DARRTS Reference ID 3635441
- Sponsor's submitted background package for NDA 207963, Palonosetron HCl
- DPMH review for Aloxi (palonosetron HCl) (NDA 21372/S-018, S-019) dated April 30, 2014, DARRTS Reference ID 3497449

Consult Question:
DGIEP requests assistance from DPMH in completing the review of the pregnancy and lactation section of labeling.

REGULATORY HISTORY

Palonosetron Hydrochloride (HCl) is a selective serotonin subtype 3 ($5HT_3$) receptor antagonist that was initially approved by the FDA on July 25, 2003, for chemotherapy-induced nausea and vomiting in adults and in 2008 for the prevention of postoperative nausea and vomiting up to 24 hours after surgery in adults. On August 7, 2014, Exela Pharma Sciences submitted a 505 (b)(2) New Drug Application (NDA) 207963 for Palonosetron HCl Injection for the proposed indication of prevention of nausea and vomiting after/during moderately and highly emetogenic cancer and chemotherapy treatments (b) (4) . The applicant is proposing a new strength for this product (0.25mg/2ml) while the active ingredient, dosage form, route of administration (b) (4)

The Division of Gastroenterology and Inborn Errors Products (DGEIP) consulted the Division of Pediatric and Maternal Health (DPMH) on September 24, 2014, to provide input for appropriate labeling of the pregnancy and lactation subsections of palonosetron injection labeling.

BACKGROUND

Palonosetron HCL and Mechanism of Action

Palonosetron HCl is a 5-HT_3 receptor antagonist with a strong binding affinity for the 5-HT_3 receptor and little or no affinity for other receptors. 5-HT_3 receptors are located on the nerve terminals of the vagus nerve in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. Nausea and vomiting is triggered by the release of 5-HT_3 in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates the 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex. [1]

Pregnancy and Lactation Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[2] also known as the Pregnancy and Lactation Labeling Rule (PLLR). 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) will be removed from all prescription drug and biological product

[1] Drugs@FDA: Aloxi (palonosetron) Labeling, Clinical Pharmacology, 12.1: Mechanism of Action, accessed 1/14/15
[2] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule[3] format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Palonosetron HCl and Pregnancy

A search of published literature for available published human pregnancy data was performed to update the Pregnancy subsection of labeling for this application. No studies or data with palonosetron use in pregnant women were found.

The current palonosetron HCl labeling provided by the sponsor includes data from animal reproduction studies that were conducted for the initial approval of palonosetron injection in 2003. In these animal studies, no fetotoxicity or teratogenicity was observed with oral administration of palonosetron to rats and rabbits during organogenesis at doses up to 1,894 and 3,789 times the recommended human intravenous dose, respectively.[4] Nonclinical studies were not submitted with this NDA because the applicant is relying on previous nonclinical findings.

Palonosetron HCl and Lactation

A search of published literature for available published human lactation data was performed to update the Lactation subsection of labeling for this application. No studies or data with palonosetron use in lactating women were found.

The rat carcinogenicity study showed that there is a potential for tumorigenicity. In a 104 week carcinogenicity study in Sprague-Dawley rats, male and female rats were given oral palonosetron at doses up to 137 and 308 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, treatment with palonosetron produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.[5]

Concerns have been raised about 5-HT3 receptor antagonists and the risk of QT interval prolongation, which is associated with an increased risk of serious ventricular arrhythmias, such as torsades de pointes.[6] The effect of palonosetron on QT interval was evaluated in a double-blind, randomized placebo controlled trial in adult men and women. The study did not show a significant effect on QTc interval prolongation with intravenous palonosetron doses up to 2.25mg. In addition, a pediatric clinical trial for the prevention of chemotherapy-induced nausea and vomiting was performed in 163 cancer patients (age range 2 months to

[3] *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).
[4] Yash, Chopra. Pharmacology/Toxicology Review of NDA 21-372 9/26/2002, pg 171-172.
[5] Drugs@FDA: Aloxi (palonosetron) Labeling, Nonclinical Toxicology: section 13.1, accessed 1/20/15
[6] Tricco, et al. Safety of serotonin (5-HT3) receptor antagonists in patients undergoing surgery and chemotherapy: protocol for a systemic review and network meta-analysis. Drug Safety and Effectiveness Network. 2013; 2:46.

16.9 years) who received a single 20 mcg/kg intravenous infusion of palonosetron 30 minutes before beginning the first cycle of chemotherapy. There was no mention of the QT interval being measured. Reported adverse events in children included headache, dizziness and dyskinesia (<1%), infusion site pain (<1%) and allergic dermatitis (<1%).[7]

Reviewer Comments
It is not known if palonosetron is present in human milk. Although rat carcinogenicity studies showed a potential risk for tumorigenicity, these effects were seen at dose exposures much higher than human exposure. In addition, the animals received multiple doses, not a single dose that would typically be used for post-operative nausea and vomiting. At this time, there are no specific safety concerns that would support a recommendation against breastfeeding.

CONCLUSIONS AND RECOMMENDATIONS
Palonosetron HCl labeling has been updated to comply with the PLLR. A review of the literature for relevant data revealed no new data with palonosetron HCl use in pregnant or lactating women. DPMH has the following recommendations for palonosetron HCl labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of palonosetron HCl labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" subsections[8].
- **Lactation, Section 8.2**
  - The "Lactation" subsection of palonosetron HCl labeling was formatted in the PLLR format to include the "Risk Summary" subsection[9].

Because the applicant has voluntarily complied with the PLLR requirements prior to the June 30, 2015 effective date, language waiving the current labeling requirements should be included in the approval letter. The following approval letter language is suggested.

"WAIVER OF PREGNANCY, LABOR AND DELIVERY, AND NURSING MOTHERS SUBSECTIONS

We are waiving the current requirements of 21CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), regarding the content and format of labeling for subsections 8.1 Pregnancy, 8.2 Labor and Delivery, and 8.3 Nursing Mothers of prescribing information. Your approved labeling for subsections 8.1, 8.2, and 8.3 reflects the content and format requirements of the Pregnancy and Lactation Labeling Rule (79 FR 72063, December 4, 2014) which implements on June 30, 2015."

[7] Drugs@FDA: Aloxi (palonosetron) Labeling, Adverse Reactions: section 6 and Clinical Pharmacology: Pharmacodynamics: Section 12.2, accessed 1/20/2015.
[8] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.
[9] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

RECOMMENDATIONS
DPMH revised subsections 8.1 and 8.2 in palonosetron labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on palonosetron use in pregnant women to inform drug-associated risks. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral palonosetron to rats and rabbits during organogenesis at doses up to 1894 and 3789 times the recommended human intravenous dose, respectively *[see Data]*. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In animal reproduction studies, no effects on embryo-fetal development were observed in pregnant rats given oral palonosetron at doses up to 60 mg/kg/day (1894 times the recommended human intravenous dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (3789 times the recommended human intravenous dose based on body surface area) during the period of organogenesis.

8.2 Lactation
Risk Summary
There are no data on the presence of palonosetron in human milk, the effects of palonosetron on the breastfed infant, or the effects of palonosetron on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for palonosetron or from the underlying maternal condition.

APPENDIX A – Applicant's Proposed Pregnancy (b) (4) Labeling

(b) (4)

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/s/

MIRIAM C DINATALE
04/28/2015

TAMARA N JOHNSON
04/28/2015

LYNNE P YAO
04/29/2015

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:	April 1, 2015
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 207963
Product Name and Strength:	Palonosetron Hydrochloride Intravenous Injection 0.25 mg/2 mL
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Exela Pharma Sciences, LLC
Submission Date:	August 7, 2014
OSE RCM #:	2014-1984
DMEPA Primary Reviewer:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Kendra Worthy, Pharm.D.

1 REASON FOR REVIEW

This review is in response to a request by DGIEP to review proposed prescribing information and container labels for any areas that may cause medication errors. Exela Pharma Sciences, LLC submitted a 505 b(2) NDA on August 7, 2014 to DGIEP.

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
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C-N/A
Human Factors Study	D-N/A
ISMP Newsletters	E
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Exela Pharma Sciences, LLC submitted a 505 (b)(2) NDA to obtain marketing approval of Palonosetron Hydrochloride injection 0.125 mg/mL. The reference listed drug for this product is Aloxi (Palonosetron Hydrochloride Injection). Aloxi is currently marketed in 0.075 mg/1.5 mL whereas Exela's formulation is 0.25 mg/2 mL (0.125 mg/mL). We reviewed the proposed prescribing information and container label and identified areas in the label and labeling that can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We note that the applicant is proposing a new strength for this product while the active ingredient, dosage form, route of administration and indication is same as the reference listed product. We have considered the risks of dosing errors with this new strength and found that there are no relevant issues since the dose is based on mg and it is clearly labeled in the prescribing information. DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide the recommendations in Section 4 to address the deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR EXELA PHARMA SCIENCES, LLC

Based on this review, we recommend the following be implemented prior to approval of this NDA:

1. Increase the prominence of the established by using larger font.
2. As currently presented, the NDC number is located (b) (4) the carton labeling. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(3)(i). Relocate the NDC number from the side panel to the top third of principal display panel.
3. As currently presented, the NDC number is denoted by a placeholder (XXXXX-XXXX-XX). Please submit the NDC number prior to approval.
4. As currently presented, there are (b) (4) Rx only statements on the side panel. Please move one statement to the bottom right corner of the principle display pane (b) (4)
5. Add a usual dosage statement to the side panel. For example, “Usual dose: See prescribing information”.
6. Remove the trailing zero from the strength presentation (0.25 mg/2 mL) to avoid misinterpretation.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Palonosetron Hydrochloride that Exela Pharma Sciences, LLC submitted on August 7, 2014, 2014.

Table 2. Relevant Product Information for Palonosetron Hydrochloride Intravenous Injection 0.25 mg /2 mL	
Initial Approval Date	N/A
Active Ingredient	Palonosetron Hydrochloride
Indication	Palonosetron Injection is a serotonin subtype 3 (5-HT3) receptor antagonist indicated in adults for: Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses. Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses. (b) (4)
Route of Administration	Intravenous
Dosage Form	Injection
Strength	0.25 mg /2 mL
Dose and Frequency	Chemotherapy-Induced Nausea and Vomiting: 0.25 mg as a single intravenous dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy. (b) (4)
How Supplied	Single (b) (4) vial individually packaged in a single carton.
Storage	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F).

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On March 24, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Palonosetron

D.2 Results

Our search identified one case, but was excluded since it was not relevant for this review.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on March 24, 2015, using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[1]

Table 3: FAERS Search Strategy	
Date Range	**January 1, 2014 to March 1, 2015**
Product	**Palonosetron** [active ingredient]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]

E.2. Results

Our search identified no cases, which described errors relevant for this review.

[1] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

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,[2] along with postmarket medication error data, we reviewed the following Palonosetron Hydrochloride labels and labeling submitted by Exela Pharma Sciences, LLC on August 7, 2014.

Prescribing Information
Container Label

G.2 Label and Labeling Images

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SHERLY ABRAHAM
04/01/2015

KENDRA C WORTHY
04/01/2015

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 # 207963 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Palonosetron Hydrochloride Injection Dosage Form: syringe/injection Strengths: 0.125 mg/mL (0.25 (b) (4) mg/ 2 mL)		
Applicant: EXELA PHARMACEUTICAL SCIENCES LLC Agent for Applicant (if applicable):		
Date of Application: August 7, 2014 Date of Receipt: August 8, 2014 Date clock started after UN: August 15, 2014		
PDUFA Goal Date: June 15, 2015	Action Goal Date (if different):	
Filing Date: October 14, 2014	Date of Filing Meeting: October 2, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5		
Proposed indication(s)/Proposed change(s): Prevention of nausea and vomiting after/during moderately and highly emetogenic cancer chemotherapy treatments (b) (4)		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ 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 ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ 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 [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ 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)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s):

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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 tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☐	☒	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
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)].**	☐	☒	☐	
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)]?** ***If you answered yes to any of the above 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***	☐	☒	☐	
Is there unexpired exclusivity on any drug product containing the 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:	☒	☐	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 21372	ALOXI	**I-684, M-136**	May 27, 2017
NDA 21372	ALOXI	**PED**	Nov 27, 2017

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

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*				
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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***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.*	☐	☐	☒	

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 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) 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
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), 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.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
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)?	☐	☒	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☐	☒		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***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…"*	☒	☐	☐	
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, 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.*	☐	☒		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	☒	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☒	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☐	☒	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☐	☒		
Is the PI submitted in 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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☒	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☒	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☐	☒	☐	
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? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) 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) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	PMHS, OSE, OPDP, PLT
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		Meeting canceled after preliminary comments on November 30, 2012
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 2, 2014

BLA/NDA/Supp #: 207963

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: Palonosetron Hydrochloride Injection

DOSAGE FORM/STRENGTH: 0.125 mg/mL (0.25 (b) (4) mg/ 2 mL)

APPLICANT: EXELA PHARMACEUTICAL SCIENCES LLC

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Prevention of nausea and vomiting after/during moderately and highly emetogenic cancer chemotherapy treatments. (b) (4)

BACKGROUND: Exela Pharma's palonosetron I.V. differs from the RLD (Aloxi I.V.) with respect to the active ingredient concentration and excipients used. To address potential safety concerns deriving from this difference, as requested by the Agency, a local irritation study has been completed and submitted.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	James Carr	Yes
	CPMS/TL:	Brian Strongin	No
Cross-Discipline Team Leader (CDTL)	Marie Kowblansky		No
Clinical	Reviewer:	Laurie Muldowney	Yes
	TL:	Ruyi He	No (Karyn Berry covering)
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		

Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sandhya Apparaju	Yes
	TL:	Sue-Chih Lee	No
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tracy Behrsing	Yes
	TL:	Sushanta Chakder	Yes
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Raymond (Ray) Frankewich/	Yes
	TL:	Marie Kowblansky	No
Quality Microbiology *(for sterile products)*	Reviewer:	Stephen Langille	Yes
	TL:	Marie Kowblansky	No
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Christina Cappaci-Daniel	Yes
	TL:	Mahesh Ramanadham	No
OSE/DMEPA (proprietary name)	Reviewer:	Sherly Abraham	Yes
	TL:	Kendra Worthy	No
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	Kareen Riviere/ Tapash Ghosh (BioPharm); Karen Dowdy (PLT)		
Other attendees	Joette Meyer, Acting Associate Director of Labeling		

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☐ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	Palonosetron Hydrochloride Injection, 0.125 mg/mL is a parenteral drug product intended for administration by injection. The proposed drug product, Palonosetron Hydrochloride Injection, 0.125 mg/mL has the same active ingredient, dosage form, route of administration (b) (4) as Helsinn Healthcare SA's listed drug product, ALOXI® (palonosetron hydrochloride) Injection, that is the subject of an approved full new drug application, NDA No. 021372. The proposed drug product differs from the reference listed drug with respect to the active ingredient concentration and inactive ingredients.

• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: Although submission did not follow eCTD submission format, the material submitted did not impede the review process of the teams and is not a cause for issue. The sponsor will be asked to submit future submission in the proper format	☐ Not Applicable
CLINICAL **Comments**: Clinical has Information Requests to be declared in the 74-day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: OSI declared NAI	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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	☒ Not Applicable ☐ YES ☐ NO

health significance? **Comments**:	
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Indicated they had some minor high level labeling issues for the 74-day letter	☐ 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

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **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>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested?	 ☒ YES ☐ NO

If no, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • 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: Division Level (TBD)

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: Mid Cycle meeting: January 15, 2015; Wrap Up meeting: May 11, 2015; Primary Reviews due by May 11, 2015; Secondary reviews by May 18, 2015.

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing.

	Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	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 NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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/s/

JAMES B CARR
02/23/2015

BRIAN K STRONGIN
02/23/2015