

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203050Orig1s000**

**OTHER REVIEW(S)**

505(b)(2) ASSESSMENT

Application Information		
NDA # 203050	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Not applicable Established/Proper Name: palonosetron hydrochloride Dosage Form: injection Strengths: 0.075 mg/1.5 mL, 0.25 mg/5 mL		
Applicant: Dr. Reddy's Laboratories Limited		
Date of Receipt: January 3, 2012. Tentatively approved November 2, 2012. Request for final approval received September 1, 2015.		
PDUFA Goal Date: March 1, 2016		Action Goal Date (if different):
RPM: Mary Chung		
Proposed Indication(s): <ol style="list-style-type: none"><li>1. Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses</li><li>2. Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses</li><li>3. Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery.</li></ol>		

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	<p>Highlights of Prescribing Information (all sections)</p> <p>Full Prescribing Information – all sections except 11 Description and 16 How Supplied/Storage and Handling Patient Labeling</p> <p>Patient Labeling – all sections except “What are the ingredients in Palonosetron Hydrochloride Injection?”</p>

\*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<sup>1</sup>. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The proposed drug product differs from the listed drug product in that it contains sodium acetate rather than sodium citrate (b) (4) and it does not contain disodium edetate (EDTA), (b) (4). The (b) (4) formulation of the proposed drug product is not expected to impact the bioavailability of palonosetron following intravenous administration. The rationale is as follows:

(b) (4)

<sup>1</sup>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.

Sodium acetate and sodium citrate (b) (4) are present in the human body; therefore, injection of the small amount of sodium acetate or sodium citrate (b) (4) present in the listed drug or the proposed drug product into the human body will not affect the pharmacologic characteristics of palonosetron.

### 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

<sup>1</sup>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").

Dr. Reddy's proposed formulation contains the same active and inactive ingredients (b)(4) as the reference product (b)(4)

(b)(4) In addition, a sodium acetate trihydrate (b)(4) is being utilized instead of (b)(4) citrate (b)(4) as in the reference product.

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

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

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

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

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

YES  NO

*If "NO" to (a) proceed to question #11.*

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

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

YES  NO

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

N/A  YES  NO

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

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

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

Pharmaceutical equivalent(s):

NDA 021372, Aloxi injection

There are 2 generic pharmaceutical equivalent products listed in the Orange Book (ANDA 202521; ANDA 90713).

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):

**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

*Below are patents listed since the November 2, 2012 Tentative Approval*

8518981

8598218

8598219

8729094

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 7947724, 7947725, 7960424**

Date(s): April 2, 2012 and April 3, 2012

Note: The NDA and patent owners [Helsinn Healthcare SA (Switzerland) and Roche Palo Alto LLC] received notifications on the dates listed above. Dr. Reddy's provided the USPS Track/Confirm and FedEx Tracking web print outs to confirm these dates. Helsinn Healthcare SA and Roche are listed as the patent owners on the patent forms.

Dr. Reddy's also informed Helsinn Therapeutics Inc. (US) via USPS on February 13, 2012. A registered mail receipt was provided for this correspondence. Dr. Reddy's again notified Helsinn Therapeutics Inc (US) via USPS on April 3, 2012 per the USPS Track/Confirm web print out.

**Regarding patents 8518981, 8598218, 8598219, 8729094**

Date(s): September 26, 2014

Note: Helsinn Healthcare SA (Switzerland) received notifications on the date listed above via UPS Tracking web print outs that contained name and date of signature. Dr. Reddy's also informed Helsinn Therapeutics Inc. (US) via USPS on the date listed above. A signed/dated registered mail receipt was provided for this correspondence to Helsinn Therapeutics Inc. (US).

Date(s): September 30, 2014

Note: Roche Palo Alto LLC received notifications on the dates listed above. Dr. Reddy's provided the USPS web print outs to confirm these dates. USPS print outs did not include proof of signature or name. However, all lawsuits have been jointly filed by both Helsinn and Roche.

**Regarding patents 9066980, 9125905, 9173942**

Date(s): January 29, 2016

Note: Helsinn Healthcare SA (Switzerland) received notifications on the date listed above. Dr. Reddy's provided the UPS web print outs to confirm these dates.

Date(s): February 10, 2016

Note: Roche Palo Alto LLC and Helsinn Therapeutics Inc. (US) received notifications on the date listed above. Dr. Reddy's provided the UPS web print outs to confirm these dates.

**Additional Note for All Patents**

It is noted that for another palonosetron application under review, the sponsor of the other application states that according to the USPTO PAIR website that the address for the patent owner or patent owner representatives is:

Trautman Sanders LLP  
600 Peachtree Street  
Suite 5200  
Atlanta, GA 30308

Dr. Reddy's did not provide notice of paragraph IV certification to Trautman Sanders.

Dr. Reddy's addressed this lack of notice per their response provided to the application on 2/18/16, which indicated Dr. Reddy's has given notices to both the patent owners(s) listed on the patent and the NDA holder(s) per 21 CFR 314.52.

- (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 May 11, 2012 for patent 7947724

Lawsuit filed on December 27, 2013 for patent 8518981, 8598218, 8598219. On May 29, 2014, lawsuit filed for patent 8518981 and 8598218 was dismissed.

Lawsuit filed on July 7, 2014 for patent 8729094

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY H CHUNG  
03/04/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

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

**NDA Number:** 203-050

**Sponsor:** Dr. Reddy's Laboratories, Inc.

**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

Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery.

**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<sup>®</sup> (palonosetron HCl) NDA 21-372 on January 3, 2012. The application received a tentative approval on November 2, 2012 because the listed drug upon which the application relied was subject to a period of patent protection. The tentatively approved labeling had the following statement in subsection 8.4 Pediatric Use.

“Safety and effectiveness in patients below the age of 18 years have not been established.”

The sponsor submitted a Request for Final Approval on September 1, 2015. In this new submission, the sponsor proposed to remove subsection 8.4 Pediatric Use entirely from the labeling.

According to the CMC reviewer, there are no excipients which represent a safety concern for pediatric patients in this formulation.

The innovator, Aloxi<sup>®</sup>, 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<sup>®</sup> for prevention of post-operative nausea and vomiting was completed, however an indication was not approved because the drug did not demonstrate efficacy. Thus, Aloxi<sup>®</sup> has the following indications:

Aloxi<sup>®</sup> is a serotonin-3 (5-HT<sub>3</sub>) 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<sup>®</sup> 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

(b) (4)



**Sponsor's request for a waiver**

The sponsor requested a waiver of pediatric studies under PREA as part of the original application in 2012.

*Reviewer comment: This application does not include a new active ingredient, a new indication, a new dosage form, a new dosing regimen or a new route of administration. Therefore the application does not trigger PREA.*

**Discussion and Recommendation**



**DPMH Recommended Labeling**  
**8.4 Pediatric Use**

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

The safety and effectiveness of Palonosetron Injection for prevention of postoperative nausea and vomiting have not been established in pediatric patients.

**Rationale**

For Chemotherapy Induced Nausea Vomiting (CINV):

Safety and effectiveness of the Aloxi<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup> and would also be established for use in this palonosetron product without additional pediatric studies if the pediatric indication was not protected. Stating 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. In addition, use of the more general indication is consistent with what DPMH is recommending for the PONV indication. Once the pediatric information is no longer protected, the specific language for the CINV indication, which is in the Aloxi<sup>®</sup> labeling, can be added to this product’s labeling.

For PONV:

An assessment of Aloxi<sup>®</sup> for the prevention of post-operative nausea and vomiting was completed, however a pediatric indication was not approved because the drug did not demonstrate efficacy. There were no safety concerns identified as a result of the pediatric study.

Additional comment:

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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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AMY M TAYLOR  
02/18/2016

JOHN J ALEXANDER  
02/18/2016

I concur with the labeling recommendations. I am also signing for Dr. Sachs.

**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 10, 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)**  
Marcia Williams, PhD  
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 203050

Applicant: Dr. Reddy's Laboratories Limited c/o Dr. Reddy's Laboratories, Inc.

## 1 INTRODUCTION

On September 1, 2015, Dr. Reddy's Laboratories Limited c/o Dr. Reddy's Laboratories, Inc. re-submitted for the Agency's review 505(b)(2) New Drug Application (NDA) 203050 for PALONOSETRON INJECTION. 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 action letter for Tentative Approval, issued on November 2, 2012. The Reference Listed Drug (RLD) is ALOXI (palonosetron HCl) Injection for Intravenous Use NDA 021372. The proposed indication for PALONOSETRON INJECTION is for the treatment of adults with:

- 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

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on October 16, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PALONOSETRON INJECTION.

## 2 MATERIAL REVIEWED

- Draft PALONOSETRON INJECTION PPI received on November 4, 2015 and received by DMPP and OPDP on February 1, 2016.
- Draft PALONOSETRON INJECTION Prescribing Information (PI) received on November 4, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 1, 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 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading 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 APFont 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.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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02/10/2016

LASHAWN M GRIFFITHS  
02/10/2016

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

Memorandum

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

**Date:** February 2, 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 203050  
OPDP Comments for draft palonosetron injection for intravenous use  
Dr Reddy's

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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 January 29, and have no additional comments. We have reviewed the draft carton/container labeling, retrieved on February 2, 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](mailto:meeta.patel@fda.hhs.gov).

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MEETA N PATEL  
02/02/2016



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:** January 20, 2016                      **Date Consulted:** October 13, 2015

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

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

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

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

**Drug:** Palonosetron Hydrochloride (HCl) Injection

**NDA:** 203050

**Applicant:** Dr. Reddy's Laboratories, Inc.

**Subject:** Pregnancy and Lactation labeling

**Proposed Indication:** Prevention of nausea and vomiting after/during moderately and highly emetogenic cancer and chemotherapy treatments and for prevention of postoperative nausea and vomiting.

**Materials Reviewed:**

- DPMH consult request dated October 13, 2015, DARRTS Reference ID 3833063
- Sponsor's submitted background package for NDA 203050, Palonosetron HCl
- DPMH review for Aloxi (palonosetron HCl) (NDA 21372/S-018, S-019). Miriam Dinatale, DO. April 30, 2014, DARRTS Reference ID 3497449



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

**Consult Question:**

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

**INTRODUCTION**

The Division of Gastroenterology and Inborn Errors Products (DGEIP) consulted the Division of Pediatric and Maternal Health (DPMH) on October 13, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of palonosetron hydrochloride labeling.

**REGULATORY HISTORY**

Palonosetron hydrochloride (HCl) is a selective serotonin subtype 3 (5HT<sub>3</sub>) 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 January 3, 2012, Dr. Reddy's Laboratories Limited, submitted a 505 (b)(2) New Drug Application (NDA) 203050 for palonosetron HCl Injection for the proposed indication of prevention of nausea and vomiting after/during moderately and highly emetogenic cancer and chemotherapy treatments and for prevention of postoperative nausea and vomiting. The reference listed product is Aloxi (palonosetron hydrochloride injection), NDA 21372. The currently proposed product does not contain disodium edetate (EDTA) and has an acetate buffer instead of the citrate buffer in Aloxi. Otherwise, the active ingredient, dosage form, route of administration and indication for palonosetron HCl are the same as Aloxi.

Palonosetron HCl was tentatively approved on November 2, 2012, because the reference listed drug was still subject to a period of patent protection. On September 1, 2015, the applicant submitted a request for final approval of palonosetron HCl.

**BACKGROUND****Palonosetron HCL and Mechanism of Action**

Palonosetron HCl is a 5-HT<sub>3</sub> receptor antagonist with a strong binding affinity for the 5-HT<sub>3</sub> receptor and little or no affinity for other receptors. 5-HT<sub>3</sub> 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<sub>3</sub> 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<sub>3</sub> receptors located on vagal afferents to initiate the vomiting reflex.<sup>1</sup>

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<sup>1</sup> Drugs@FDA: Aloxi (palonosetron) Labeling, Clinical Pharmacology, 12.1: Mechanism of Action, accessed 1/14/15

## **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*,”<sup>2</sup> 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) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule<sup>3</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

## **DISCUSSION**

### **Palonosetron HCl and Nonclinical Findings**

The current palonosetron HCl labeling provided by the applicant includes data from animal reproduction studies that were conducted for the initial approval of palonosetron injection in 2003. In these animal studies, no embryo-fetotoxicity 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.<sup>4</sup>

The rat carcinogenicity study showed 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.<sup>5</sup> Nonclinical studies were not submitted with this NDA because the applicant is relying on previous nonclinical findings from the reference listed drug.

### **Palonosetron HCl and Pregnancy**

A search of published literature for available human pregnancy data was performed to update the Pregnancy subsection of labeling for this application. No studies or data with the use of palonosetron or other 5HT<sub>3</sub> receptor antagonists, including dolasetron, or granisetron, in pregnant women were found in PubMed or Embase. However, there were studies that evaluated another 5HT<sub>3</sub> receptor antagonist, ondansetron, and use in pregnant women, and clinical studies with ondansetron have demonstrated mixed results as described below.

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<sup>2</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>3</sup> *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).

<sup>4</sup> Yash, Chopra. Pharmacology/Toxicology Review of NDA 21-372 9/26/2002, pg 171-172.

<sup>5</sup> Drugs@FDA: Aloxi (palonosetron) Labeling, Nonclinical Toxicology: section 13.1, accessed 1/20/15

Some human studies have failed to demonstrate an increased risk of fetal malformations, spontaneous abortions, stillbirths, preterm delivery, delivery of a low-birth-weight infant, or delivery of a small-for-gestational-age infant with first trimester ondansetron use.<sup>6,7,8</sup> However, other human studies have suggested a potential association between first-trimester ondansetron use and fetal malformations (cleft palate and cardiac malformations).<sup>9,10,11</sup> FDA is continuing to review the safety of ondansetron.

### Summary

Overall, there is no evidence of embryo-fetotoxicity in animal reproduction studies performed with palonosetron. There are no human data on palonosetron use in pregnant women. There are several published studies on use of ondansetron, another drug in the same class as palonosetron, during pregnancy. At the current time, these studies have not conclusively identified a specific safety concern. (b) (4)

Therefore, at the present time, the content of palonosetron pregnancy labeling will remain unchanged.

### **Palonosetron HCl and Lactation**

A search of published literature for available human lactation data was performed to update the Lactation subsection of labeling for this application. No studies or data with palonosetron or ondansetron use in lactating women were found in the Drugs and Lactation Database (LactMed),<sup>12</sup> PubMed, or Embase.

In Medications and Mother's Milk<sup>13</sup>, Dr. Hale, a breastfeeding expert, notes that palonosetron works similarly to ondansetron. Although there are no data on the transfer of palonosetron into human milk, palonosetron does not cause major adverse effects in patients who have taken the drug.

<sup>6</sup> Einarson, et al. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG*. 2004; 111: 940-943.

<sup>7</sup> Pasternick, B. Svanstrom, H, Hviid, A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N. Engl J Med*. 2013. 368(9): 814-823.

<sup>8</sup> Asker C, Norstedt W, Kallen B. Use of antiemetic drugs during pregnancy in Sweden. *European Journal of Clinical Pharmacology*. 2005; 61:899 -906.

<sup>9</sup> Anderka, et al. Medications Used to Treat Nausea and Vomiting of Pregnancy and the Risk of Selected Birth Defects. *Birth Defects Research*. 2011.; 94: 22-30.

<sup>10</sup> Anderson, et al. Ondansetron use in early pregnancy and the risk of congenital malformations. *Int Soc Pharmacoepidemiol*. 2013. Abstract 25.

<sup>11</sup> Danielsson, et al. Use of ondansetron during pregnancy and congenital malformations in the infant. *Reprod Toxicol*. 2014; 50: 134-137.

<sup>12</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

<sup>13</sup> Hale, T. Medications and Mother's Milk. Hale Publishing, 2012.

Concerns have been raised about 5-HT<sub>3</sub> 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.<sup>14</sup> 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 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%).<sup>15</sup>

### Summary

It is not known if palonosetron is present in human milk. Although rat carcinogenicity studies (see “Palonosetron HCl and Nonclinical Findings” above) 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 new safety concerns that would support a change in recommendations regarding breastfeeding. Therefore, the Risk/Benefit statement in the Lactation section of labeling as required under PLLR will state the following:

“The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for palonosetron and any potential adverse effects on the breastfed infant from palonosetron or from the underlying maternal condition.”

### **Palonosetron and Females and Males of Reproductive Potential**

A search of PubMed and Embase was performed for available published data on palonosetron-related effects on fertility using the search terms “palonosetron and infertility” “palonosetron and reproduction”, and “palonosetron and sperm.” No data were found.

In animal studies, oral palonosetron, at doses 1894 times the recommended human intravenous dose, was found to have no effect on fertility and reproductive performance of male and female rats.

### Summary

There are no human data on the effects of palonosetron on fertility and no evidence of infertility in animal studies. Therefore, section 8.3, Females and Males of Reproductive Potential, will not be included in palonosetron labeling.

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<sup>14</sup> Tricco, et al. Safety of serotonin (5-HT<sub>3</sub>) 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.

<sup>15</sup> Drugs@FDA: Aloxi (palonosetron) Labeling, Adverse Reactions: section 6 and Clinical Pharmacology: Pharmacodynamics: Section 12.2, accessed 11/18/2015.

## CONCLUSIONS

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<sup>16</sup>.

- **Lactation, Section 8.2**

- The “Lactation” subsection of palonosetron HCl labeling was formatted in the PLLR format to include the “Risk Summary” subsection<sup>17</sup>.

## 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.

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<sup>16</sup> 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.

<sup>17</sup> 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.

## DPMH Proposed Palonosetron HCL Pregnancy and Lactation 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 a drug-associated risk. 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 and any potential adverse effects on the breastfed infant from palonosetron or from the underlying maternal condition.

#### Patient Information

**Before receiving palonosetron hydrochloride injection, tell your doctor about all of your medical conditions, including if you:**

- are pregnant or plan to become pregnant. It is not known if palonosetron hydrochloride injection will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if palonosetron hydrochloride injection passes into your breast milk. (b) (4)

[REDACTED]

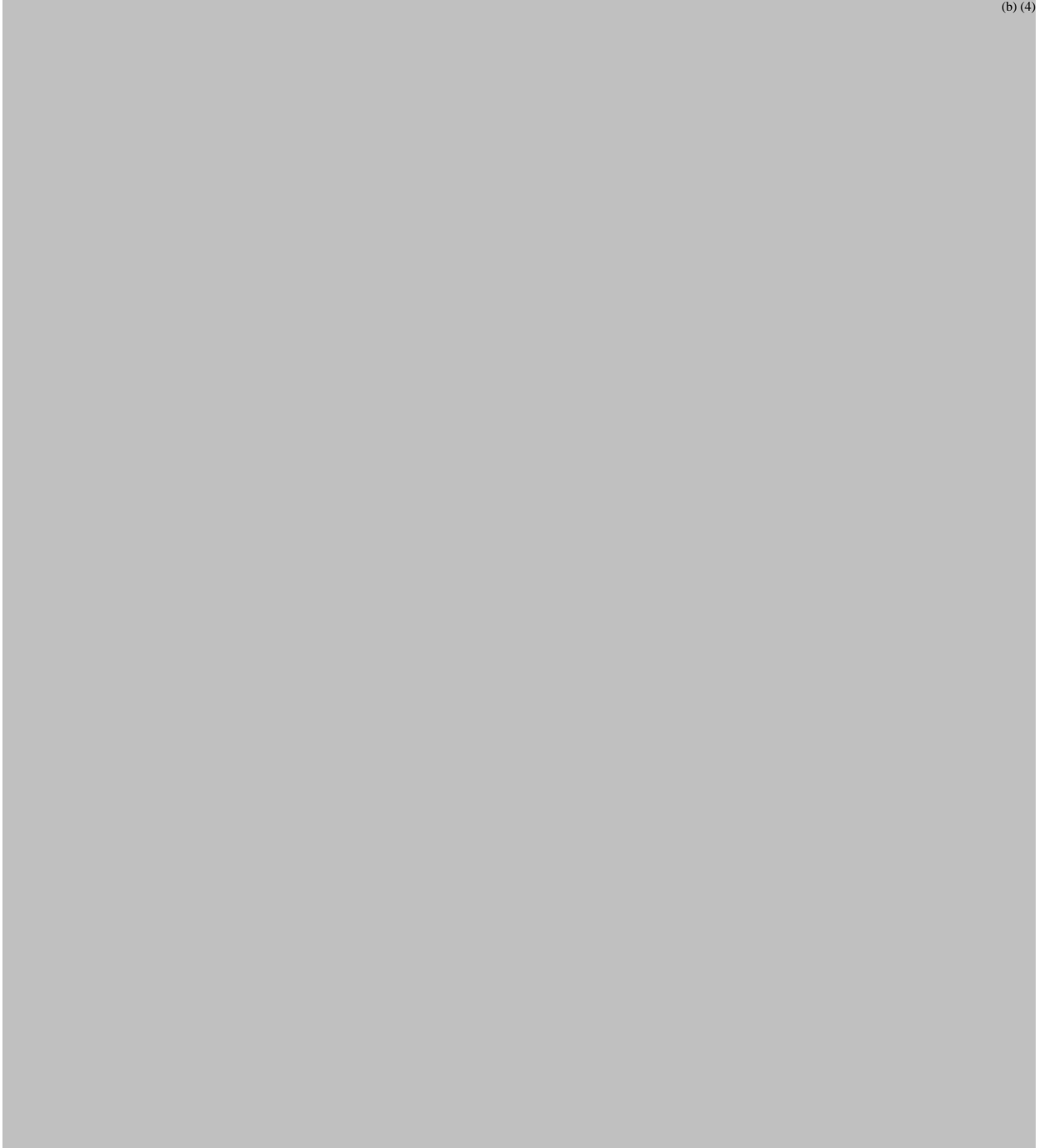
**APPENDIX A – Applicant’s Proposed Palonosetron HCL Pregnancy and Lactation Labeling**

**FULL PRESCRIBING INFORMATION**

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

(b) (4)



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MIRIAM C DINATALE  
01/20/2016

TAMARA N JOHNSON  
01/20/2016

LYNNE P YAO  
01/25/2016



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## **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\*\*\***

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**Date of This Review:** January 19, 2016

**Requesting Office or Division:** Division of Gastroenterology and Inborn Error Products (DGIEP)

**Application Type and Number:** NDA 203050

**Product Name and Strength:** Palonosetron Hydrochloride Injection  
0.075 mg/1.5 mL and 0.25 mg/5 mL

**Product Type:** Single Ingredient

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Dr. Reddy's Laboratories, Inc.

**Submission Date:** September 1, 2015

**OSE RCM #:** 2015-2760

**DMEPA Primary Reviewer:** Sherly Abraham, R.Ph.

**DMEPA Team Leader:** Mishale Mistry, Pharm.D., MPH

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## 1 REASON FOR REVIEW

This review is in response to a request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) to review the proposed Prescribing Information, container labels, and carton labeling for any areas of vulnerability that may lead to medication errors. The proposed labels and labeling were submitted as an amendment to NDA 203050, on September 1, 2015 to request a final approval of labeling, CMC, and patent information, from a previous tentative approval on November 2, 2012.

## 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.

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

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Dr. Reddy's Laboratories, Inc. submitted a 505(b)(2) NDA to obtain marketing approval of Palonosetron Hydrochloride injection, 0.075 mg/1.5 mL (0.05 mg/mL) and 0.25 mg/5 mL (0.05 mg/mL). The Reference Listed Drug (RLD) for this product is Aloxi (Palonosetron Hydrochloride Injection). We note that the applicant is proposing the same active ingredient, strength, dosage form, and route of administration 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 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. We note that the Applicant for the proposed palonosetron product is not pursuing the pediatric indication for CINV. DMEPA reviewed the proposed labels and labeling to determine

whether there are any significant concerns in terms of safety, related to preventable medication errors. Although the proposed Prescribing Information is acceptable, we identified areas in the label and labeling that can be improved to increase the readability and prominence of important information and promote the safe use of the product. We provide the recommendations in Section 4.1 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 DR. REDDY'S LABORATORIES, INC.

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

###### Carton and container labels:

1. Revise the font color of the established name (blue color) or revise the color scheme of the strengths (b) (4) color), (b) (4)  
The use of the (b) (4) color font for the established name and the product strengths minimize the difference between the strengths, which may lead to wrong strength selection errors
2. There is inadequate differentiation between the 0.075 mg/1.5 mL and 0.25 mg/5 mL strengths. Consider (b) (4) increasing the font size or some other means to provide adequate differentiation between the vial and container labels.
3. For the vial labels, consider decreasing the prominence of the storage statement by decreasing the font size. Established name and strength should be the most prominent information on the vial and container labels.
4. As currently presented, the product code in the NDC number for 0.25 mg/5 mL strength (b) (4) the product code in the NDC number for 0.075 mg/1.5 mL strength (b) (4). This can lead to wrong strength errors because barcode scanners may only read (b) (4) the NDC codes (i.e. (b) (4)) and pharmacists may rely on the (b) (4) portion as a manual check. Therefore, we recommend that you revise the product code in the NDC numbers (b) (4).
5. Add a net quantity statement to the principal display panel (PDP) in accordance with 21 CFR 201.51. We recommend that the net quantity statement be located away from the

product strength and with less prominence. For example, the statement can be added to the bottom right corner of the PDP across from the Rx only statement with same font size and type as the “Rx only” statement.

6. Delete the (b) (4) statement (b) (4)
7. Revise the (b) (4) statement to “Single dose vial(s)” since the term “single dose” accurately describes the correct usage of this product in a single patient as a single injection.<sup>1</sup>
8. If space permits, consider adding the usual dosage statement on the side panel of the vial label. For example, “Usual dose: See prescribing information”.

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<sup>1</sup> <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 Dr. Reddy’s Laboratories, Inc. submitted on September 1, 2015.

<b>Table 2. Relevant Product Information for Palonosetron</b>	
<b>Initial Approval Date</b>	<b>N/A</b>
<b>Active Ingredient</b>	Palonosetron Hydrochloride
<b>Indication</b>	<p>Palonosetron Injection is a serotonin subtype 3 (5-HT<sub>3</sub>) receptor antagonist indicated in adults for:</p> <p>Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses.</p> <p>Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses.</p> <p>Prevention of postoperative nausea and vomiting (PONV) for upto 24 hours following surgery.</p>
<b>Route of Administration</b>	Intravenous
<b>Dosage Form</b>	Injection
<b>Strength</b>	0.25 mg/5 mL 0.075 mg/1.5 mL
<b>Dose and Frequency</b>	<p>Chemotherapy-Induced Nausea and Vomiting:</p> <p>Adults: 0.25 mg as a single intravenous dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy.</p> <p style="text-align: right;">(b) (4)</p> <p>Postoperative Nausea and Vomiting:</p> <p>0.075 mg as a single intravenous dose administered over 10 seconds immediately before the induction of anesthesia.</p>
<b>How Supplied</b>	0.25 mg/5 mL-single (b) (4) vial individually packaged in a carton.

	0.075 mg/1.5 mL-single (b) (4) vial package in a carton containing 5 vials.
<b>Storage</b>	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 B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On January 5, 2016, we searched the L: drive and AIMS using the terms, Palonosetron (Dr.Reddy's) to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified one previous review<sup>2</sup>, and we confirmed that our previous recommendations were implemented or considered.

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<sup>2</sup> Baugh,D. Label and Labeling Review for Palonosetron Hydrochloride Injection NDA 203050. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 09 28. RCM No.: 2012-1296

## APPENDIX D. ISMP NEWSLETTERS

### D.1 Methods

On December January 7, 2016, 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.

<b>ISMP Newsletters Search Strategy</b>	
<b>ISMP Newsletter(s)</b>	Acute care, Community, and Nursing
<b>Search Strategy and Terms</b>	Match Exact Word or Phrase: Palonosetron

### D.2 Results

Our search identified one case, but was excluded since it was not associated with the current labels and labeling for Palonosetron.



## APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

### E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on January 7, 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<sup>3</sup>

<b>Table 3: FAERS Search Strategy</b>	
<b>Date Range</b>	<b>January 1, 2014 to January 1, 2016</b>
<b>Product</b>	<b>Aloxi [Product name] Palonosetron [active ingredient]</b>
<b>Event (MedDRA Terms)</b>	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

### E.2. Results

Our search did not identify any relevant cases associated with the current labels and labeling for Palonosetron.

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<sup>3</sup> 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>.

### **E.3 Description of FAERS**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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/s/  
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SHERLY ABRAHAM  
01/19/2016

MISHALE P MISTRY  
01/19/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # 203050	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Palonosetron Hydrochloride Dosage Form: Injection Strengths: 0.075 mg/1.5 mL and 0.25 mg/5mL		
Applicant: Dr. Reddy's Laboratories Limited		
Date of Receipt: January 3, 2012		
PDUFA Goal Date: November 3, 2012		Action Goal Date (if different): November 2, 2012
Proposed Indications: 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 3. The prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.		

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 or by reliance on published literature. *(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 referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of 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 – all sections except “What are the ingredients in Palonosetron Hydrochloride Injection?”

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Dr. Reddy’s indicates that (b) (4) qualitative composition of their proposed products (b) (4) as the composition of the reference Aloxi (palonosetron hydrochloride) injection, (b) (4) In comparison to the reference Aloxi injection, Dr. Reddy’s product also proposes the same conditions of use, active ingredient, route of administration, dosage form, and dose strengths. Dr. Reddy’s palonosetron formulation is also equivalent to the reference Aloxi product with respects to critical quality parameters including osmolarity, pH, and impurities.

Based on this information, Dr. Reddy’s requested a waiver of the in vivo bioequivalence study requirements as allowed under 21 CFR 320.22(b)(1)(i) and (ii). According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. A drug product’s in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients (b) (4) as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

Per review of the supporting information in this application, the request for waiver of in vivo BE study requirements is granted.

### 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 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

### 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 referenced the 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/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	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 monograph?  
 YES  NO   
*If "YES", please list which drug(s).*  
 Name of drug(s) described in a 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").

Dr. Reddy's proposed formulation contains the same active and inactive ingredients (b) (4) as the reference product (b) (4). (b) (4) sodium acetate trihydrate (b) (4) is being utilized instead of (b) (4) citrate (b) (4) as in the reference product.

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 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)).**

**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?

YES  NO



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 approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

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)?

YES  NO

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):

**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

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): April 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

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

YES  NO

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

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

YES  NO

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

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

Date(s): April 2, 2012 and April 3, 2012

Note: The NDA and patent owners [Helsinn Healthcare SA (Switzerland) and Roche Palo Alto LLC] received notifications on the dates listed above. Dr. Reddy's provided the USPS Track/Confirm and FedEx Tracking web print outs to confirm these dates. Helsinn Healthcare SA and Roche are listed as the patent owners on the patent forms.

Dr. Reddy's also informed Helsinn Therapeutics Inc. (US) via USPS on February 13, 2012. A registered mail receipt was provided for this correspondence. Dr. Reddy's again notified Helsinn Therapeutics Inc (US) via USPS on April 3, 2012 per the USPS Track/Confirm web print out.

(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 May 11, 2012 on for patent 7947724.

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/s/  
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JAGJIT S GREWAL  
11/01/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: September 28, 2012

Reviewer: Denise V. Baugh, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, MS  
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Palonosetron Hydrochloride Injection  
0.075 mg/1.5 mL and 0.25 mg/5 mL

Application Type/Number: NDA 203050

Applicant: Dr. Reddy's Laboratories

OSE RCM: 2012-1296

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Palonosetron Injection (NDA 203050) for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

This NDA is a 505(b)(2) application and the reference listed drug (RLD) is Aloxi (Palonosetron Hydrochloride) Injection (NDA 021372) approved July 25, 2003. The composition of the Applicant's product is the same as the reference listed drug (b) (4) DMEPA was notified by the Division of Gastroenterology and Inborn Errors Products (DGIEP) via e-mail August 7, 2012 that there are no safety concerns with regard to this difference. The active ingredient, concentration, indications, dose and administration, preparation instructions, dosage form, and route of administration are the same as the reference listed drug.

### 1.2 PRODUCT INFORMATION

The following product information is provided in the January 3, 2012 label and labeling submission.

- Active Ingredient: Palonosetron Hydrochloride
- Indication of Use: prevention of nausea and vomiting associated with initial and repeated courses of moderately emetogenic and highly emetogenic chemotherapy; prevention of postoperative nausea and vomiting for up to 24 hours after surgery
- Route of Administration: intravenous
- Dosage Form: single (b) (4) vial
- Strength: 0.25 mg/5 mL and 0.075 mg/1.5 mL
- Dose and Frequency:

Indication	Dose
Chemotherapy-Induced Nausea and Vomiting	A single 0.25 mg intravenous dose given over 30 seconds approximately 30 minutes before the start of chemotherapy
Postoperative Nausea and Vomiting	A single 0.075 mg intravenous dose given over 10 seconds immediately prior to the induction of anesthesia

- How Supplied: 0.075 mg/1.5 mL - packaged in a carton containing 5 vials; 0.25 mg/5 mL - packaged in a carton containing 1 vial
- Storage: 20°C to 25°C (68°F to 77°F) – (b) (4) protect from freezing, protect from light
- Container and Closure System: clear, colorless solution packed in 2 mL and 5 mL USP Type-1 tubular glass with 13 mm and 20 mm grey, rubber stopper



## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (AERS) database for the reference listed drug, Aloxi (Palonosetron Injection) for any medication error reports involving this product because errors may also occur with the proposed drug product. We also reviewed the Palonosetron Injection container labels, carton and insert labeling submitted by the Applicant.

### 2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1.

<b>Table 1: AERS Search Strategy</b>	
Date	August 4, 2012 (no time limitations were used)
Drug Names	Active Ingredient: Palonosetron Trade Name: Aloxi Verbatim terms: Aloxi% and Palonos%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The AERS database search identified 2 cases. Both cases were reviewed for relevancy and duplication. After individual review, one case was excluded from the final analysis (as it was an adverse event related to a concomitant medication and unrelated to Aloxi) and one medication error case remained for our detailed analysis.

This case was a wrong dose medication error in which the patient received the intravenous dose of Aloxi 0.25 mg twice within 24 hours resulting in a total dose of 0.5 mg. No adverse reactions were noted. No other details regarding contributing factors or the final patient outcome was provided. We note that the insert labeling for Aloxi (Palonosetron Hydrochloride) is clear with regard to the frequency of administration of this drug product and this information is similarly stated in the labeling for the proposed Palonosetron Injection.

### 2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted January 3, 2012 (Appendix A)
- Carton Labeling submitted January 3, 2012 (Appendix B)

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Insert Labeling submitted January 3, 2012 (no image)

### 3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The product proposed by the Applicant differs from the reference listed drug (RLD) in that it contains sodium acetate rather than sodium citrate (b)(4) and it does not contain disodium edetate (EDTA). However, there is no safety concern if this proposed drug product is used instead of Aloxi based upon our discussion with the Division. All product characteristics are the same for both products (e.g., indication, dose, route and frequency of administration, preparation instructions, concentration and packaging configurations). Additionally, the Applicant has not submitted a proprietary name for this product.

The color scheme for the proposed container label and carton labeling of the Dr. Reddy products for the two different vial sizes (0.075 mg/1.5 mL and 0.25 mg/5 mL) is adequately differentiated. However, there is a (b)(4) graphic on the principal display panel which clutters the label and labeling. Although this design (b)(4) is problematic on small volume parenteral vials where there is limited space to convey important drug identifying information. See Section 5 for our recommendations for improvement.

### 4 CONCLUSIONS

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

### 5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. General Comments (All Container Labels and Carton Labeling)
  1. Remove (b)(4) principal display panel so that important drug identifying information can be presented without a cluttered appearance. (b)(4) design is problematic for small volume vial sizes with limited space.
- B. Container Label (1.5 mL and 5 mL Single Dose Vials )
  1. Revise and relocate the statement “ (b)(4) to read “For Intravenous Use” and to appear below the concentration (‘0.05 mg/mL’) to improve its visibility and readability.
  2. Revise the statement (b)(4) to read ‘Single- (b)(4) Vial’ and relocate this statement to appear after the statement, ‘For Intravenous Use’. The word (b)(4) is an assumed characteristic of an injectable product and the volume, (‘1.5 mL’ and

‘5 mL’) is included in the total drug content and therefore they are unnecessary statements.

3. Add the statement (b) (4) to follow the statement ‘Single (b) (4) Vial’ to reinforce proper handling of this product.
4. Delete the statement (b) (4) from the side panel for the 1.5 mL vial size (see recommendation above).
5. To make room for important information on the principal display panel and to minimize clutter, revise the salt ‘Hydrochloride’ to read ‘HCL’.
6. To make room for important information on the principal display panel, consider making the blue graphic (b) (4) smaller/thinner.

The following is an example of how the information may appear on the principal display panel (based upon recommendations 1 to 3 and 5):

Palonosetron HCL Injection  
0.25 mg/5 mL  
(0.05 mg/mL)  
For Intravenous Use Only  
Single (b) (4) Vial. (b) (4)

C. Carton Labeling (five 1.5 mL vials and 5 mL Single Dose Vials)

1. Revise the statement (b) (4) to read “Five Single (b) (4) Vials”. The word (b) (4) is an assumed characteristic of an injectable product and the volume, (‘1.5 mL’) is already included in the total drug content and therefore both of these statements are unnecessary.
2. Revise the statement (b) (4) to read “Single- (b) (4) Vial”. The word (b) (4) is an assumed characteristic of an injectable product and the volume, (‘5 mL’) is already included in the total drug content and therefore both of these statements are unnecessary.
3. Revise the statement (b) (4) to read “For Intravenous Use”.

D. Insert Labeling

1. The abbreviation “I.V” is used by the Applicant through out the insert labeling. The abbreviation “I.V” can be misinterpreted to mean I.U (International Units) or mistaken for the Roman numeral ‘four’. Due to the continuing confusion between “IV” and other abbreviations, we recommend that “IV” be replaced with the text “intravenous”. As part of a national campaign to decrease the use of error prone abbreviations, acronyms, dose designations, or symbols, FDA agreed to not use such error prone designations in the approved labeling of products.

If you have further questions or need clarifications, please contact Nitin Patel, OSE Project Manager, at 301-796-5412.

## **APPENDICES**

### **APPENDIX A. DATABASE DESCRIPTIONS**

#### **Adverse Event Reporting System (AERS)**

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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**Table 2:** ISR numbers of case discussed in this review

<b>ISR #, Date Received, Gender/Age, Country</b>	<b>Medication Error Type</b>	<b>Contributing Factors</b>	<b>Outcome</b>	<b>Narrative</b>
5126863, 08/04/2006, 43 year old/female, USA	Improper Dose leading to Overdose	Unknown	No adverse reactions were noted. Patient discharged home (final outcome not stated)	Patient received Aloxi 0.25 mg intravenous push for chemotherapy anti-emetic prophylaxis on [REDACTED] (b) (6) and then received an additional dose on the same day for a total of 0.5 mg. Concomitant medications included Zantac, dexamethasone, and paclitaxel. No adverse reactions were noted. The patient was made aware and informed of possible side effects to look for. Patient was discharged home.

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/s/  
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DENISE V BAUGH  
09/28/2012

LUBNA A MERCHANT  
10/01/2012

SCOTT M DALLAS  
10/01/2012

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

**PATIENT LABELING REVIEW**

Date: August 9, 2012

To: Donna Griebel, MD  
Director  
**Division of Gastroenterology and Inborn Error Products  
(DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

From: Nathan Caulk, MS, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling: Patient Package Insert  
(PPI)

Drug Name (established name): Palonosetron Hydrochloride

Dosage Form and Route: injection, for Intravenous Use

Application Type/Number: NDA 203-050

Applicant: Dr. Reddy's Laboratories



## 1 INTRODUCTION

On January 3, 2012, Dr. Reddy's Laboratories submitted for the Agency's review an Original 505(b) (2) New Drug Application (NDA) 203-050. The Reference Listed Drug (RLD) is ALOXI (palonosetron HCl), NDA 21-372. The proposed indication for palonosetron hydrochloride injection is indicated 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
- the prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery.

On June, 5, 2012, the Division of Gastroenterology and Inborn Error Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for palonosetron hydrochloride injection.

This review is written in response to a request by DGIEP for DMPP to review the Applicant's proposed PPI for palonosetron hydrochloride injection.

## 2 MATERIAL REVIEWED

- Draft palonosetron hydrochloride injection PPI received on January 3, 2012.
- Draft palonosetron hydrochloride injection Prescribing Information (PI) received on January 3, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on July 30, 2012.
- Approved ALOXI (palonoestron hydrochloride injection) comparator labeling dated February 29, 2008.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> 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 APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP 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.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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NATHAN P CAULK  
08/09/2012

SHARON R MILLS  
08/09/2012

LASHAWN M GRIFFITHS  
08/10/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion  
Division of Consumer Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** August 3, 2012

**To:** Jagjit Grewal, Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**From:** Kathleen Klemm, Regulatory Review Officer  
Division of Professional Drug Promotion (DPDP)  
Office of Prescription Drug Promotion (OPDP)

Kendra Y. Jones, Regulatory Review Officer  
Division of Consumer Drug Promotion (DCDP)

**Subject:** NDA 203050  
OPDP labeling comments for Palonosetron Hydrochloride Injection  
for intravenous use

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OPDP has reviewed the proposed Prescribing Information (PI) and Patient Information (PPI) for Palonosetron Hydrochloride Injection for intravenous use (palonosetron) submitted for consult on June 5, 2012.

OPDP notes that the proposed PI and PPI for palonosetron is substantially similar to the currently approved PI and PPI for the referenced product NDA 021372 Aloxi (palonosetron HCl) Injection.

OPDP has no comments on the proposed PI and PPI at this time. This review is based on the version of the proposed PI and PPI for palonosetron sent via email from Jagjit Grewal (RPM) on July 30, 2012, that is provided directly below.

Thank you for the opportunity to comment on this label. If you have any questions regarding this proposed draft PI, please contact Katie Klemm at 301-796-3946 or [Kathleen.klemm@fda.hhs.gov](mailto:Kathleen.klemm@fda.hhs.gov).

If you have any questions regarding this proposed draft PPI, please contact Kendra Jones at 301-796-3917 or [Kendra.jones@fda.hhs.gov](mailto:Kendra.jones@fda.hhs.gov).

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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KENDRA Y JONES  
08/03/2012

KATHLEEN KLEMM  
08/03/2012

## 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 # 203050 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Palonosetron Hydrochloride Dosage Form: Injection Strengths: 0.075 mg/1.5mL and 0.25 mg/5 mL		
Applicant: Dr. Reddy's Laboratories Limited Agent for Applicant (if applicable): Dr. Reddy's Laboratories, Inc.		
Date of Application: January 3, 2012 Date of Receipt: January 3, 2012 Date clock started after UN: N/A		
PDUFA Goal Date: November 3, 2012	Action Goal Date (if different): November 2, 2012	
Filing Date: March 3, 2012	Date of Filing Meeting: February 15, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5		
Proposed indication(s)/Proposed change(s): New formulation which includes changes in buffering and chelating agents.		
<ul style="list-style-type: none"> <li>• Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses</li> <li>• Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses</li> <li>• Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.</li> </ul>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:  <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>                      and refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug	

	<input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)								
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)								
Collaborative Review Division ( <i>if OTC product</i> ):									
List referenced IND Number(s): N/A									
<b>Goal Dates/Product Names/Classification Properties</b>									
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<table border="1"> <thead> <tr> <th>YES</th> <th>NO</th> <th>NA</th> <th>Comment</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">X</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	YES	NO	NA	Comment	X			
YES	NO	NA	Comment						
X									
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<table border="1"> <thead> <tr> <th>YES</th> <th>NO</th> <th>NA</th> <th>Comment</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">X</td> <td></td> <td></td> <td>No proprietary name is proposed by the applicant.</td> </tr> </tbody> </table>	YES	NO	NA	Comment	X			No proprietary name is proposed by the applicant.
YES	NO	NA	Comment						
X			No proprietary name is proposed by the applicant.						
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)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<table border="1"> <thead> <tr> <th>YES</th> <th>NO</th> <th>NA</th> <th>Comment</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">X</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	YES	NO	NA	Comment	X			
YES	NO	NA	Comment						
X									
<b>Application Integrity Policy</b>									
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>	<table border="1"> <thead> <tr> <th>YES</th> <th>NO</th> <th>NA</th> <th>Comment</th> </tr> </thead> <tbody> <tr> <td></td> <td style="text-align: center;">X</td> <td></td> <td></td> </tr> </tbody> </table>	YES	NO	NA	Comment		X		
YES	NO	NA	Comment						
	X								
If yes, explain in comment column.									
If affected by AIP, has OC/DMPQ 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?		X			
<b>User Fee Status</b>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> 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?			X		
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)].			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?  <i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>			X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>			X		
<b>If yes, please list below:</b>					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>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 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					



Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></i>		X		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDA</i> s/ <i>NDA</i> efficacy supplements only)  If yes, # years requested:  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDA</i> s only)?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> 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? <sup>1</sup> If not, explain (e.g., waiver granted).	X			
<b>Index:</b> Does the submission contain an accurate comprehensive index?				

<sup>1</sup>  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

	X			
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:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>	X			
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>			X	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>		X		Sponsor did not submit or conduct any clinical studies to support the change in formulation.
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is</i>	X			

<i>included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>			X	
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>			X	Sponsor did include a request for full waiver of pediatric studies, but this application does trigger PREA.
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>		X		
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>		X		

4

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

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b>		X		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** February 15, 2012

**BLA/NDA/Supp #:** NDA 203050

**PROPRIETARY NAME:** N/A

**ESTABLISHED/PROPER NAME:** Palonosetron Hydrochloride

**DOSAGE FORM/STRENGTH:** Injection 0.075 mg/1.5mL and 0.25 mg/5 mL

**APPLICANT:** Dr. Reddy's Laboratories Limited

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

New formulation (b) (4)

- 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.

**BACKGROUND:**

On January 3, 2012, Dr. Reddy's Labs submitted a 505(b)(2) NDA 203050 Palonosetron Hydrochloride Injection. This application proposes a change in the formulation from the currently approved reference product Aloxi (palonosetron hydrochloride) Injection. The differences between Dr. Reddy's formulation and the innovator Aloxi injection product (b) (4) are outlined below: The specific formulation changes are

**Comparison of Composition of Dr. Reddy's product with RLD**

Ingredient	RLD Composition (Aloxi®)	Dr. Reddy's Formulation	Function
	Qty(mg/mL)	Qty(mg/mL)	
Palonosetron Hydrochloride	(b) (4)	(b) (4)	Active Pharmaceutical ingredient (b) (4)
Mannitol	(b) (4)	(b) (4)	
Edetate Disodium (EDTA)	(b) (4)	(b) (4)	
Sodium Acetate Trihydrate	(b) (4)	(b) (4)	
(b) (4) Citrate (b) (4)	(b) (4)	(b) (4)	
(b) (4)	(b) (4)	(b) (4)	
(b) (4)	(b) (4)	(b) (4)	

Water for Injection	(b) (4)	
Sodium Hydroxide	q.s to adjust the pH of 4.5 to 5.5	For pH adjustment
Hydrochloric acid	q.s to adjust the pH of 4.5 to 5.5	For pH adjustment
(b) (4) Palonosetron hydrochloride is equivalent to 0.05 mg of Palonosetron		

The proposed indications are the same as for the approved Aloxi injection product (prevention of acute CINV-MEC, acute & delayed CINV-MEC, and PONV).

The NDA is comprised primarily of chemistry information to support the change in formulation. No clinical or non-clinical studies have been conducted by the applicant. Additionally, the applicant requested a waiver of in-vivo bioequivalence study requirements.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jagjit Grewal	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Marie Kowblansky		Y
Clinical	Reviewer:	Karyn Berry	Y
	TL:	Ruyi He	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Kristina Estes	Y
	TL:	Sue Chih Lee	N
Biostatistics	Reviewer:		
	TL:		



Nonclinical (Pharmacology/Toxicology)	Reviewer:	Babatunde Akinshola	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for BLAs/BLA efficacy supplements)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Bogdan Kurtyka	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology <i>(for sterile products)</i>	Reviewer:	Steven Donald	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Zhong Li	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Mark Seggel, ONDQA/Biopharm Reviewer		Y

Other attendees	Donna Griebel, Director, DGIEP Andrew Mulberg, Deputy Director, DGIEP Nitin Patel, OSE RPM	
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**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p>List comments: None</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p>Comments: None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p>If no, explain: No clinical studies were conducted in support of the application. The sponsor has requested a biowaiver.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:

<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b> None</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter

<b>REGULATORY PROJECT MANAGEMENT</b>																					
<p><b>Signatory Authority:</b> To be determined (Donna Griebel, DGIEP Director or Andrew Mulberg, DGIEP Deputy Director)</p> <p><b>21<sup>st</sup> Century Review Milestones</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 2px;">60-Day Filing Date</td> <td style="width: 50%; padding: 2px;">March 3, 2012</td> </tr> <tr> <td style="padding: 2px;">74-Day Letter</td> <td style="padding: 2px;">March 17, 2012</td> </tr> <tr> <td style="padding: 2px;">Mid-cycle meeting</td> <td style="padding: 2px;">~ June 3, 2012</td> </tr> <tr> <td style="padding: 2px;">Primary reviews due</td> <td style="padding: 2px;">September 29, 2012</td> </tr> <tr> <td style="padding: 2px;">Wrap-up meeting</td> <td style="padding: 2px;">~ September 29, 2012</td> </tr> <tr> <td style="padding: 2px;">Secondary reviews due</td> <td style="padding: 2px;">October 6, 2012</td> </tr> <tr> <td style="padding: 2px;">Send PMC/PMR &amp; labeling to sponsor</td> <td style="padding: 2px;">October 6, 2012</td> </tr> <tr> <td style="padding: 2px;">CDTL Review Due</td> <td style="padding: 2px;">October 13, 2012</td> </tr> <tr> <td style="padding: 2px;">Begin PMC/PMR &amp; labeling discussions</td> <td style="padding: 2px;">October 13, 2012</td> </tr> <tr> <td style="padding: 2px;">PDUFA</td> <td style="padding: 2px;">November 3, 2012</td> </tr> </table>		60-Day Filing Date	March 3, 2012	74-Day Letter	March 17, 2012	Mid-cycle meeting	~ June 3, 2012	Primary reviews due	September 29, 2012	Wrap-up meeting	~ September 29, 2012	Secondary reviews due	October 6, 2012	Send PMC/PMR & labeling to sponsor	October 6, 2012	CDTL Review Due	October 13, 2012	Begin PMC/PMR & labeling discussions	October 13, 2012	PDUFA	November 3, 2012
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<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>																					
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:																				
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>																				
<b>ACTIONS ITEMS</b>																					
<input checked="" type="checkbox"/>	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).																				
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).																				

<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"><li>• 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)</li><li>• notify OMPQ (so facility inspections can be scheduled earlier)</li></ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	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 at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

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Regulatory Project Manager

Date

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Chief, Project Management Staff

Date

### **Appendix A (NDA and NDA Supplements only)**

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAGJIT S GREWAL  
03/14/2012

BRIAN K STRONGIN  
03/14/2012

# REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

**Application:** NDA 203050

**Name of Drug:** Palonosetron Hydrochloride Injection, 0.075 mg/1.5mL and 0.25 mg/5 mL

**Applicant:** Dr. Reddy's Laboratories Limited

## Labeling Reviewed

**Submission Date:** January 3, 2012

**Receipt Date:** January 3, 2012

## Background and Summary Description

NDA 203050 Palonosetron Hydrochloride Injection provides for a new formulation of palonosetron for the following 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
- Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

The change in formulation from the innovator Aloxi product includes:

-  (b) (4)



## Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

1. The Highlights Limitation Statement is included twice at the beginning of the package insert label.
2. The proposed label includes the “Recent Major Changes” section in highlights. This section only applies to NDA supplements, and should therefore be removed.
3. The statement regarding reporting of “Suspected Adverse Reactions” is repeated twice in highlights.
4. The header “(b) (4)” should be removed from the Table of Contents.
5. The header (b) (4) should be removed from the Table of Contents.
6. The reference statement regarding FDA-approved patient labeling should be revised to read “See FDA-approved patient labeling (Patient Information)”.
7. Patient Information should not be a subsection under the Patient Counseling Information section. Rather, it should be included at the end of section 17 without numbering as a subsection.

### **Conclusions/Recommendations**

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by April 6, 2012. The resubmitted labeling will be used for further labeling discussions.

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Regulatory Project Manager	Date
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Chief, Project Management Staff	Date
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## **Selected Requirements for Prescribing Information (SRPI)**

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## **Contents: Table of Contents (TOC)**

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection 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.”

## Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- For the “Clinical Trials Experience” subsection, 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 clinical practice.”
- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:
  - “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.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
  - “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAGJIT S GREWAL  
03/14/2012

BRIAN K STRONGIN  
03/14/2012