CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203050Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA	203050
Applicant Name	Dr. Reddy's Laboratories Ltd.
Date of Submission	September 1, 2015
PDUFA Goal Date	March 1, 2016
Proprietary Name / Established (USAN) Name	Palonosetron Hydrochloride Injection/palonosetron
Dosage Forms / Strength	Solution/ 0.25 mg/5 mL and 0.075 mg/1.5 mL in single (b) (4) vial
Proposed Indications	1. Moderately emetogenic cancer chemotherapy - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses. (in adults) 2. Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses (in adults) 3. Postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. (in adults)
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
CDTL	Original review: Marie Kowblansky, PhD Current review: Danuta Gromek-Woods, PhD
Medical Officer Review	Original review: Karyn Berry, MD/Ruyi He, MD Current review: Anil Rajpal, MD
Pharmacology Toxicology Review	Original review: B. Emmanuel Akinshola, Ph.D./ Sushanta Chakder, Ph.D. Current review: NA
CMC Review/OBP Review	Original review: Bogdan Kurtyka, Ph.D./Moo Jhong Rhee, Ph.D. Current review: See table below
Clinical Pharmacology Review	Original review: Kristina Estes, PharmD./Sue-Chih Lee, Ph.D. Current review: Sandhya Apparaju, PhD/Sue Chih Lee, PhD
DPMH	Current review: Amy M. Taylor, MD, MHS/Hari Cheryl Sachs, MD/John J. Alexander, MD, MPH

	Miriam Dinatale, DO/Tamara Johnson, MD/Lynne Yao, MD
DMPP	Current review: Karen Dowdy, RN, BSN/Marcia Williams, PhD/LaShawn Griffiths, MSHS-PH, BSN, RN
OPDP	Current Review: Meeta Patel, PharmD
OSE/DMEPA	Original review: Denise Baugh, PharmD, BCPS/Scott Dallas, RPh Current review: Sherly Abraham, RPh/ Mishale Mistry, PharmD, MPH

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DPMH=Division of Pediatric and Maternal Health
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion

Current submission:

Office of Product Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus, Ph.D.	Branch II/New Drug API
Drug Product	Zhengfang Ge, Ph.D.	ONDP/DIVISION II/BRANCH V
Process	N/A	
Microbiology	David Bateman, Ph.D.	OMPT/CDER/OPQ/OPF/DMA/MABII I
Facility	Xiaohui (Sherry) Shen	OMPT/CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Truong Quach, Pharm.D.	OPRO/Branch I
Application Technical Lead	Danuta Gromek-Woods, Ph.D.	OMPT/CDER/OPQ/ONDP/DNDPI
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue	OGROP/ORA/OO/OMPTO/DMPTPO/ MDTP
Environmental Assessment (EA)	N/A	

Division Director Review

1. Introduction

A tentative approval letter for this 505(b)(2) NDA was issued on November 2, 2012. The NDA could only be tentatively approved for the following reasons, which are stated in the November 2, 2012 tentative approval letter:

> The listed drug upon which your application relies is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act [21 U.S.C.355(c)(3)] may not be made effective until the period has expired.
>
> Furthermore, your application contains certifications to three patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("Paragraph IV certifications").
>
> Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be taken prior to the expiration of forty-five days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3) of the Act.
>
> In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patent 7,947,724 in the United States District Court, District of New Jersey (Case 3:12-cv-02867-MLC-DEA). Therefore, final approval cannot be granted until:
>
> 1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
>
>   b. the date the court decides that the patent is invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or,
>
>   c. the listed patent has expired, and
>
> 2. we are assured there is no new information that would affect whether final approval should be granted.

The applicant submitted an amendment requesting Final Approval on September 1, 2015, as the applicant believed that the conditions for final approval are now met.

2. Background

In the original review of this 505(b)(2) application, all disciplines recommended approval. There were no PMCs or PMRs recommended. PREA did not apply because the product does not contain a new active ingredient, is not a new dosage form or new route of administration. A new indication was not proposed, and a new dosing regimen was not proposed. See my original review.

The November 2, 2012 tentative approval letter stated that the amendment requesting Final Approval should provide "the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and Risk Evaluation and Mitigation Strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly." The applicant submitted this information. The legal/regulatory basis for the request for final approval was evaluated by CDER's 505b2 committee. [See Section 11 Other Regulatory Issues of this review]. The safety update was evaluated by the Clinical team leader. The labeling was reviewed by a multidisciplinary team of reviewers. Key updates to labeling in this review cycle included revisions to Sections 8.1 and 8.2, as well as Section 8.4. [See Section 10 Pediatrics and Section 12 Labeling of this review.] Furthermore, because the applicant proposed addition of a new alternate manufacturing site for drug substance (also supplied by Dr. Reddy's Laboratories Limited) in this amendment, the Product Quality Team conducted a review to assess whether manufacture at the new facility could be approved. [See Section 3 CMC of this review.]

3. CMC

I concur with the ONDQA Quality review team's conclusions regarding the acceptability of the manufacturing of the drug product. The applicant proposed a new drug substance manufacturing site in this amendment, and withdrew the original drug substance manufacturing site from the NDA. The manufacturing process, in-process controls and final drug substance specifications followed at both manufacturing sites (the original approved and the newly proposed alternate) were found to be the same, and the physico-chemical equivalence of the drug substance batches manufactured at both sites established that the drug substance quality at both sites is equivalent. The Assessment of Facitilities review noted that the originally proposed drug substance manufacturing site had been inspected in November 2014. A 483 was issued, and the outcome was OAI. A Warning Letter was sent to the firm in November 2015. The applicant proposed the alternate site, provided 3 batches of drug product using the API manufactured by the new facility, and withdrew the original site from the NDA. The new site was found to have "a long compliant inspectional history since 2000." An

inspection of this new site had been conducted in May 2014, and resulted in a final outcome of VAI. The facilities assessment team concluded, "Because drug substance manufacturing operations have been consistently and routinely covered on inspections and no significant deficiencies have been identified, this new facility is considered to be acceptable for the responsibilities proposed in this application."

There were no changes proposed in manufacturing process, excipients, container closure system, storage conditions and limits of finished product release and stability specification of the drug product. However, the newly submitted stability data now support 24-months expiration dating. An unknown impurity was noted in the original NDA submission review, which was identified at highest concentration of (b) (4)% at (b) (4) months (b) (4) . The impurity was attributed to the stopper. The reviewers at that time concluded that the specification levels for this impurity were adequate to assure safety of the product. In my original review, I noted that the reviewers stated that the stability data (and impurity level) supported (b) (4) months expiration dates; the applicant has now submitted data from samples obtained at 18 months in two batches and 24 months in one batch, which revealed lower levels of the unknown impurity, i.e., (b) (4)%. (The CDTL confirmed that these data included data from samples obtained from product stored (b) (4) .) The applicant has not proposed a change in the specification for the unknown impurity from that deemed acceptable in the original application. The reviewer stated, "However, all remaining samples were found well below specification limit for this unknown impurity during 24 months of long term storage." The levels were "well within the specification." The reviewer concluded, "Since the applicant found the root cause of this impurity, and the impurity only observed in random samples and does not constitute a significant change, it does not effect of the overall drug product stability."

Additional stability data (3 months duration) from product manufactured at the new site were reviewed. Because "no trends of changes have been observed in the 3 month stability data of drug product manufactured with the API from the alternative API manufacturing site", the CMC reviewer concluded that the addition of an alternate manufacturing site should not impact expiration dating.

4. Nonclinical Pharmacology/Toxicology

See my original review. The Pharmacology/Toxicology reviewers reassessed the product label in the review of this amendment. They worked with the Maternal and Fetal health reviewers to update the label to PLLR format.

5. Clinical Pharmacology

My original review stated the following in the Clinical Pharmacology section:

> "The ONDQA Biopharmaceutics reviewers granted a waiver of in vivo bioequivalence studies based on CFR 320.22(b), which states that 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. In their review they explain that the criteria for "self-evidence" in this situation are:

1) a parenteral solution intended solely for administration by injection, and
2) the product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

The proposed product is intended for administration by injection, has the same concentration of active ingredient and only differs from the reference Aloxi product in that it contains sodium acetate rather than sodium citrate (b) (4) does not contain EDTA. The Biopharmaceutics reviewers determined that "the in vivo BA/BE of the proposed Palonosetron HCl Injection drug product is self-evident, and the Applicant's request for a biowaiver for their proposed Palonosetron HCl Injection drug product is acceptable and the biowaiver is granted." I concur. (b) (4)

In light of the biowaiver, no clinical pharmacology studies were submitted for review. The Clinical Pharmacology reviewers recommended approval. They noted that the absence of EDTA in the proposed product (relative to the reference product) is not expected to impact pharmacological characteristics of the product or to impact efficacy."

During this review cycle, OCC and ORP (see Section 11 Other Regulatory Issues) noted that because the new proposed product does not contain all the same inactive ingredients in the same concentrations as the referenced product, the criteria outlined under CFR 320.22 have not been met. The Biopharmaceutics reviewers responded that the proposed drug product contains the same drug concentration as the referenced product Aloxi, is isotonic (like Aloxi) and has the same pH range as Aloxi (4.5-5.5); however, it differs from Aloxi in that it contains sodium acetate instead of sodium citrate (b) (4) and it does not contain EDTA. The reviewer documented in a memo, filed on March 1, 2016, that these differences would not be expected to affect the pharmacologic characteristics of palonosetron and would not be expected to result in differences in relative bioavailability. They stated the following:

"Although the criteria for a biowaiver under 21 CFR 320.22(b)(1) is not fully met, based on 21 CFR 320.24(b)(6), the FDA can rely on any other approach deemed adequate by FDA to establish the bridge (bioavailability/bioequivalence) (b) (4) the formulation of the proposed drug product is not expected to impact the bioavailability of palonosetron following intravenous administration. (b) (4)

(b) (4)

Absence of EDTA would not be expected to alter the pharmacologic activity of the product.[1]

Sodium acetate and sodium citrate (b) (4) are present in the human body; therefore, injection of a small amount of either 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. Based on the overall supportive information, it is expected that the bioavailability of the proposed and listed drug products will be similar.

In conclusion, in the Original Biopharmaceutics Review dated 6/21/2012, consistent with 21 CFR 320.24(b)(6) the FDA deemed adequate the information supporting the relative bioavailability (or bridge) to the Agency's finding of safety and effectiveness for the listed drug."

Therefore, there is sufficient information to bridge to the Agency's previous finding of safety and effectiveness for the listed drug Aloxi to support approval of the current 505(b)(2) application.

The Clinical Pharmacology reviewers reassessed the product label in the review of this amendment. They recommended revisions to make the label consistent with the PLR format. Their recommendations were incorporated.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

See my original review.

8. Safety

See my original review. The applicant submitted a safety update that consisted of a summary of their review of the medical literature for new safety reports from January 2012 to February 2016. They reported no new safety findings that should be incorporated in labeling. There were three serious adverse events reported in the literature: seizures, QTc prolongation and anaphylaxis. Anaphylaxis is already included in the palonosetron label. Palonosetron has been studied in a thorough QT study and no significant prolongation was noted. The results of a thorough QT study are included in palonosetron product labeling. Seizures are not currently listed in the palonosetron product label. The applicant identified a single case report from Korea, reported in 2012) of a patient who received palonosetron 0.075 mg IV dose in the

setting of postoperative nausea and vomiting[1] after ureteroscopy and lithotripsy. The event occurred 17 minutes after infusion and during an attempt to use a bedpan for a bowel movement. A second episode occurred >40 minutes later, after the patient had been discharged and was waiting for radiography immediately post discharge. I conducted a PubMed search with terms "palonosetron and seizure" and identified one additional report[2] from 2009 of a seizure in a patient who received palonosetron in the setting of chemotherapy induced nausea and vomiting. The event occurred 1 hour after the dose in the fourth cycle of chemotherapy, and occurred during infusion of 5-FU. Palonosetron was not administered during the following two cycles of chemotherapy and there was no recurrence of seizure activity. The Division will monitor post marketing reports further and will consider adding seizures to labeling if additional reports are received.

It should be noted that the Clinical reviewers used the approved Aloxi labeling as a guide to assess and revise the label for the new product proposed in the 505(b)(2) NDA. Any palonosetron safety issues that have been addressed by the review division in the interim and placed in the Aloxi label were also incorporated in the product label for Palonosetron Hydrochloride. For example, on September 18, 2014, there was a safety labeling change to the Aloxi label pertaining to the risk of serotonin syndrome, i.e., a Warning and Precaution stating that serotonin syndrome has been reported with 5-HT3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application. The product is not an NME.

10. Pediatrics

See my original review, appended to this review. PREA does not apply. The Division of Pediatric and Maternal Health (DPMH) was consulted during the review of the current amendment to advise the review team on appropriate pediatric labeling for this 505(b)(2) product. In the interim since the tentative approval in 2012, the listed product, Aloxi, received pediatric exclusivity (on April 10, 2014) and was approved (on May 27, 2014) for chemotherapy induced nausea and vomiting in pediatric patients ages 1 month to less than 17 years. (Aloxi also carries a postoperative nausea and vomiting (PONV) indication in adults; however, the pediatric PONV trials submitted for review did not establish efficacy and the product was not granted a pediatric PONV indication.) The tentatively approved label for this 505(b)(2) NDA, appended to the November 2, 2012 approval letter, stated in Section 8.4 Pediatric Use, that "Safety and effectiveness in patients below the age of 18 years have not been established." In this amendment, the applicant proposed a revised label that eliminated Section 8.4 Pediatric Use. The DPMH staff stated that Section 8.4 Pediatric Use cannot be removed from the label and recommended inclusion of the following information in Section 8.4:

(b) (4)

[2] Zambelli A, et al. Support Care Cancer (2009) 17:217.

> "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."

Taking into consideration the pediatric exclusivity associated with the Aloxi CINV indication, the DPMH staff based this recommendation on the fact that a statement that safety and effectiveness of palonosetron has not been established would not be true. The proprietary name of the proposed 505(b)(2) product is "Palonosetron Hydrochloride", which is the established name of Aloxi. Therefore, insertion of the proprietary name for this NDA in the statement regarding CINV could cause confusion. The DPMH staff noted that an alternative statement, "this product has not been approved for pediatric use" is true, and is allowable under regulations. The DPMH reviewers confirmed with the Office of Chief Counsel (OCC) that this language is acceptable. (Email to Amy Taylor from DPMH and Maria Walsh from ODE III dated February 25, 2016.) Since Aloxi does not carry a pediatric PONV indication, the DPMH reviewers recommended the standard pediatric language utilized in those circumstances (as noted above). The Patient Package Insert (PPI) was revised accordingly.

11. Other Relevant Regulatory Issues

CDER 505(b)(2) committee met on February 16, 2016 to discuss this application and issued an information request to the applicant to clarify an issue identified in the Committee's review. The applicant responded. The Committee reviewed the response and informed the Division in an email dated February 29, 2016 (3:46 PM; Mary Ann Holovac) that the response was adequate to address the 505(b)(2) regulatory issues related to the requirement for the applicant to provide notifications to the patent owner(s) and NDA holder.

During the review of the issues raised in a pending citizen petition regarding a different 505(b)(2) NDA for palonosetron, the FDA considered whether those issues would also implicate FDA's approval of this current NDA (203050) from Dr. Reddy's Laboratories. OCC and ORP agreed with the Division that the issues raised by the petition do not implicate the current NDA; however, they noted that the reviews for the current NDA state that a biowaiver was granted, and informed the Division that the regulatory record needed to be clarified, as the conditions of CFR 320.22(b) had not been met (the proposed product and the referenced product do not contain the same inactive ingredients). The Biopharmaceutics reviewers responded with a memo acknowledging the differences in inactive ingredients, but concluding that the differences would not be expected to impact the pharmacologic characteristics of the products; therefore, an in vivo bioequivalence study is not necessary to create a scientific bridge to the reference product to support approval. (See Section 5 Clinical Pharmacology.) OCC and ORP reviewed the memo before it was filed to this NDA on March 1, 2016.

12. Labeling

The DPMH Maternal Health Team was consulted to review the pregnancy and lactation section of product labeling submitted in this amendment. They provided recommendations for updating the label (Section 8.1 and 8.2) to comply with the PLLR (Pregnancy and Lactation Labeling Rule). Their recommendations were incorporated.

The Office of Prescription Drug Promotion was consulted to evaluate the product label submitted in this amendment. Their recommendations were incorporated in label negotiations. Reviewers from the Division of Medical Policy Programs and the Office of Prescription Drug Promotion reviewed the patient package insert (PPI), and their joint recommendations were incorporated in the final labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - approval
- Risk Benefit Assessment – There are no new risk/benefit concerns raised in the review of this amendment that would preclude granting the applicant's request for final approval.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None
- Recommendation for other Postmarketing Requirements and Commitments - None

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/s/

DONNA J GRIEBEL
03/01/2016