CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203050Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 12, 2016
From	Danuta Gromek-Woods, Ph.D., CMC Lead CDER/ONDP/Division II/Branch V
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 203050
Applicant	Dr. Reddy's Laboratories Ltd.
Date of Submission	September 1, 2015
PDUFA Goal Date	March 1, 2016
Proprietary Name / Established (USAN) names	Palonosetron Hydrochloride Injection (palonosetron hydrochloride)
Dosage forms / Strength	Solution/ 0.25mg/5mL & 0.075mg/1.5mL in single dose vials (b) (4)
Proposed Indication(s)	Adults • 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
Recommended:	Approval

1. Introduction

Palonosetron Hydrochloride Injection is intended for use in the prevention of nausea and vomiting in patients undergoing chemotherapy. The product will be manufactured in single (b) (4) vials containing either 0.25mg/5mL or 0.075mg/1.5mL of palonosetron, (b) (4) (Both strengths contain 0.05 mg palonosetron per milliliter of solution.) In addition to palonosetron hydrochloride, the product also contains mannitol (b) (4) sodium acetate (b) (4) water for injection, sodium hydroxide or hydrochloric acid (pH adjustment), (b) (4) It will be manufactured by Gland Pharma Limited (b) (4) India.

This NDA has been filed as a 505(b)(2) application, using Aloxi® (palonosetron hydrochloride) Injection, manufactured by Helsinn Healthcare under NDA 21-372 as the listed drug. The proposed drug product has the same route of administration, dosage form, active ingredient, strengths, and indications as Aloxi®. While Dr. Reddy's formulation is similar to Aloxi in a number of ways, (b) (4) it contains sodium acetate instead of the sodium citrate (b) (4) in Aloxi) and does not contain EDTA. (The listed drug contains (b) (4) EDTA.) Biopharmaceutics reviewers have concluded that this difference in formulation is not expected to impact pharmacologic characteristics of the product and the relative bioavailability is expected to be comparable. (b) (4)

Reference ID: 3895251

There is no IND associated with the application and no clinical data have been submitted; for approval of this product, the sponsor is relying on previous findings of efficacy and safety for Aloxi®.

There were no unresolved issues or deficiencies that needed to be conveyed to the sponsor during the review of original application. No PMRs, PMCs, or pediatric studies need to be requested.

The overall recommendation was that the original NDA 203050, submitted on 03-Jan-2012, should be approved. This conclusion was based on recommendations from all disciplines involved in the review of this application. However, due to the unexpired patents for Aloxi®, a tentative approval was recommended at that time, with the earliest possible approval date being April 13, 2015, when US Patent No. 5,202,333 was expiring.

A tentative Approval Letter was sent to the applicant on 02-Nov-2012, stating the following:

"To obtain final approval of this application, submit an amendment two or six months prior to the:
1) expiration of the period of patent or exclusivity protection or 2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL."** … Until we issue a final approval letter, this NDA is not deemed approved".

On 01-Sep-2015, sponsor submitted their Request for Final Approval which includes CMC amendments and proposed labeling changes. This CDTL review summarizes findings related to the applicant's Request for Final Approval amendment.

2. Background

Palonosetron is a serotonin 5-HT3 receptor antagonist that functions as an antiemetic and antinauseant agent. It was approved in 2003 as the hydrochloride salt in Aloxi® (palonosetron hydrochloride) Injection and has been marketed by Helsinn Healthcare since that time. Its indications are for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy, prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy as well as for the prevention of postoperative nausea and vomiting for up to 24 hours following surgery. Administration instructions call for intravenous administration, and limit the dose to no more than 0.25 mg per day. Helsinn also has FDA approval for an oral capsule formulation of Aloxi® containing 0.5mg palonosetron, but this product is not marketed in the US. For the oral product, administration instructions call for one capsule one hour prior to chemotherapy.

As discussed above, except for the absence of EDTA and the substitution of sodium acetate for sodium citrate buffer, the composition and strength of the current product is (b) (4) innovator. It is due to the absence of EDTA in this Dr. Reddy's product that the current NDA has been submitted as a 505(b)(2) application, instead of a 505(j).

3. CMC

As noted in the Introduction, there were no unresolved CMC issues that would have precluded the approval of the original application from the CMC perspective, according to the CMC reviewer, Dr. Bogdan Kurtyka (see review in DARRTS dated 22-Oct-2012). NDA was tentatively approved on 02-Nov-2012 because of an existing patent protection for the listed reference application and a patent infringement suit.

This CDTL review summarizes findings related to the applicant's Request for Final Approval submitted on 01-Sep-2015, with the following new CMC information for the drug substance and the drug product:

Drug Substance:
Request for Final Approval provides for an addition of alternate manufacturing site (b) (4) for drug substance (palonosetron hydrochloride) supplied by the same manufacturer (Dr. Reddy's Laboratories Limited) under the same DMF (# 23590). Dr. Reddy's proposes to use the API supplied from the alternate manufacturing facility only for the future commercial supplies. The applicant references the Type II DMF 23590 for details on the description, characterization, manufacture, packaging, specification for quality control testing, and stability of the proposed drug substance, palonosetron hydrochloride.

The manufacturing process, in-process controls and final drug substance specifications followed at both the manufacturing sites are same. The physico-chemical equivalence of the drug substance batches manufactured at both the sites (b) (4) is demonstrated to show that the quality of the drug substance manufactured at both sites is equivalent. DMF 23590 has been recently reviewed as Adequate (2-Dec-2015 by J. Leginus).

Drug Product:
- Information on three commercial scale batches of drug product by using the drug substance manufactured at the alternate site (b) (4).
- Extension of expiration dating period of drug product Palonosetron Hydrochloride Injection, from (b) (4) months to 24 months based on additional long term stability data.
- The comparative data for the new drug product batches manufactured using (b) (4) API and the original submission batches manufactured using (b) (4) API. To evaluate the impact of API site change on quality of the drug product, Dr. Reddy's has manufactured three commercial scale validation batches of drug product with (b) (4) Liter batch size using the drug substance manufactured at the alternate site (b) (4) and evaluated them against the original submission batches.

There is no change in qualitative & quantitative composition, manufacturing process, excipients, container closure system, storage conditions, and limits of finished product release & stability specifications of the drug product.

Based on review of the Drug Substance reviewer, Dr. J. Leginus, the data are adequate to support the use of palonosetron hydrochloride drug substance from the alternative supplier in the manufacture of palonosetron drug product.

As per review of the Drug Product Reviewer, Dr. Zhengfang Ge, the stability data submitted in this application are adequate to support the proposed 24-months expiration dating period and to demonstrate that the newly added drug substance manufacturer does not impact the previous Approval recommendation of this application.

The Division of Microbiology issued an approvable recommendation as well.

Based on the Facility Assessment, there appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the involved facility's inspection results, inspectional history, and relevant experience. The Office Process and Facility made a recommendation of approval for Palonosetron Hydrochloride Injection 0.075 mg/1.5 mL and 0.25 mg/5 mL.

In conclusion, as per Review #2 in panorama, dated 09-Feb-2016, all involved OPQ disciplines recommended an approval of NDA 203050.

4. Nonclinical Pharmacology/Toxicology

As stated in the CDTL review dated 31-Oct-2012, Dr. B. Emmanuel Akinshola, the nonclinical pharmacology/toxicology reviewer, has concluded that from a nonclinical pharmacology standpoint, the original NDA is approvable. No new nonclinical toxicology studies were conducted in connection with this NDA; the safety of palonosetron hydrochloride has been established from the toxicology studies conducted by the innovator in different species. There are no safety concerns for this new formulation of palonosetron hydrochloride.

No new nonclinical information was submitted since the Tentative Approval.

5. Clinical Pharmacology/ Biopharmaceutics

Historically, Dr. Kristina Estes, the Clinical Pharmacology reviewer has judged the original application to be acceptable for approval from the viewpoint of the Office of Clinical Pharmacology. According to her review, "(b) (4) does not contribute to the efficacy of palonosetron and the absence of this (b) (4) in the proposed product is not expected to alter the efficacy of intravenous palonosetron."

Dr. Mark Seggel, ONDQA Biopharmaceutics reviewer, granted a waiver of *in vivo* bioequivalence studies on the basis that the bioequivalence of the current drug product and the RLD is self evident. Based on Biopharmaceutics considerations, this NDA was recommended for approval.

Although the criteria for a biowaiver under 21 CFR 320.22(b)(1) were not fully met, based on 21 CFR 320.24(b)(6), the FDA can rely on any other approach deemed adequate by FDA to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products. While Dr. Reddy's formulation is similar to Aloxi in a number of ways, (b) (4) it contains sodium acetate instead of the sodium citrate (b) (4) in Aloxi) and does not contain EDTA. Biopharmaceutics reviewers have concluded that this difference in formulation is not expected to impact pharmacologic characteristics of the product and the relative bioavailability is expected to be comparable. Thus 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 Dr. Reddy's application. An in vivo pharmacokinetic study is not needed to establish a scientific bridge to Aloxi.

No new clinical pharmacology information was submitted since the Tentative Approval.

As per review of the current submission "Request for Final Approval", the clinical pharmacology reviewer, Dr. Sandhya Apparaju, the proposed drug product labeling has been reviewed by DCP3 and modifications were proposed to make it consistent with the PLR format. Clinical Pharmacology/Biopharmaceutics maintain the original approvable recommendation.

6. Clinical Microbiology

Not Applicable

7. Clinical

The route of administration, indication, and dosage of Dr. Reddy's formulation are the same as ALOXI®, the listed drug. Because of the bioequivalence of the two formulations, the applicant did

not conduct any clinical trials for this application, instead referencing the Agency's previous findings of safety and efficacy for ALOXI®.

(b) (4)

In her Clinical Review from the original NDA submission, Dr Karyn Berry, recommended approval of this application for the same indications and target populations as ALOXI® Injection. However, now that palonosetron has a pediatric CINV indication, the proposed drug product cannot have the pediatric indication due to exclusivity, see Section 10. No post-market risk evaluation and/or mitigation have been recommended.

No clinical evaluation was made during the current review cycle of the Final Request for Approval, as there weren't any clinical trials submitted with this Request for Final Approval.

8. Safety

Palonosetron is a drug with widespread distribution and, according to the medical review, has a generally good safety profile. Please refer to the Clinical review of the original NDA submission.

There are no new safety concerns, as no new safety information was submitted since the Tentative Approval.

9. Advisory Committee Meeting

Not Applicable

10. Pediatrics

The applicant requests a waiver of pediatric assessment requirements for all pediatric age groups, in accordance with section 505B (a)(4)(A)(iii) of the Act. The rationale is that palonosetron fails to represent a meaningful therapeutic advance over existing therapies already approved for use in pediatric age groups for chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV), and thus is unlikely to be used in a substantial number of pediatric patients.

This NDA does not propose a product that contains a new active ingredient, new indications, new dosage forms, new dosing regimens, or new routes of administration compared to the listed drug, ALOXI. Therefore, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the applicant is not required to evaluate the use of Palonosetron Hydrochloride injection in the pediatric population.

However, the listed drug, NDA 21372 Aloxi (palonosetron) I.V., has a pediatric indication that is protected by pediatric exclusivity. Therefore, DPMH has recommended the appropriate language for subsection 8.4 of the product label that is within the constraints of 505(b)(2) regulations.

11. Other Relevant Regulatory Issues

During the review of the original NDA, the listed drug application, NDA 21372 ALOXI® (palonosetron hydrochloride) Injection, had four unexpired patents listed in the Orange Book:

- US Patent No. 5,202,333 - Expiry Date: April 13, 2015

- US Patent No. 7,947,724 - Expiry Date: Jan. 30, 2024
- US Patent No. 7,947,725 - Expiry Date: Jan. 30, 2024
- US Patent No. 7,960,424 - Expiry Date: Jan. 30, 2024

On May 11, 2012, the patent holder filed a suit against Dr. Reddy's laboratories for infringement of patent 7,947,724. The application could only be tentatively approved at that time.

Since the Tentative Approval, the applicant had additional patent infringement suits The 505(b)(2) Committee reviewed the information regarding the patents and lawsuits and has determined that this application can be approved at this time.

12. Labeling

During the current review cycle, the labeling review includes the package insert (PI) and Patient Package Insert (PPI). FDA proposed PI and PPI have been issued to the applicant on 11-Feb-2016.

As per Label and Labeling review from Division of Medication Error Prevention and Analysis (DMEPA), prepared by Sherly Abraham, R.Ph., DMEPA concluded that the proposed label and labeling can be improved to increase readability and prominence of important information on the label to promote the safe use of the product.

Pre-decisional agency memo in DARRTS, prepared by Meeta Patel, PharmD, Office of Prescription Drug Promotion (OPDP), states that "OPDP has reviewed the proposed draft PI, and carton/container labeling for palonosetron injection for intravenous use" and have no additional comments.

As per Patient Labeling Review from Division of Medical Policy Programs (DMPP), prepared by Karen Dowdy, the PPI is acceptable with recommended changes addressed to the applicant.

Division of Pediatric and Maternal Health (DPMH) issued a Memorandum on pregnancy and lactation labeling. The review of Miriam Dinatale, D.O., Medical Officer, Maternal Health, concludes that a review of the literature for relevant data revealed no new data with palonosetron HCl use in pregnant or lactating women. DPMH revised subsections 8.1 and 8.2 in palonosetron labeling for compliance with the PLLR. DPMH refers to the final NDA action for final labeling.

DPMH has recommended the appropriate language for subsection 8.4 that is within the constraints of 505(b)(2) regulations.

13. Recommendations/Risk Benefit Assessment

An injectable palonosetron hydrochloride product has been marketed in the US since 2003 under the tradename ALOXI®. The availability of Dr. Reddy's currently proposed product, Palonosetron Hydrochloride Injection would provide an alternative formulation that contains the same amount of the active ingredient as the ALOXI® product, but without EDTA. Differences between the two intravenously administered products would not be expect to impact the relative safety and efficacy associated with these products.

There are no unresolved issues or deficiencies that need to be conveyed to the sponsor. No PMRs, PMCs, or pediatric studies need to be requested.

The overall recommendation is that this NDA should be approved. This conclusion is based on recommendations from all disciplines involved in the review of the original submission and this Request for Final Approval application.

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/s/

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