

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203050Orig1s000

MEDICAL REVIEW(S)

Date	(electronic stamp)
From	Anil Rajpal, MD, MPH
Subject	Safety Update Discussion
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

Overview

The applicant submitted a safety update that consisted of a summary of their review of the medical literature for new safety reports from the interim period between the tentative approval date and the resubmission.

Safety Update

The November 2, 2012 tentative approval letter indicated “In addition to a safety update, the amendment [“request for final approval”] should also identify changes, if any, in the conditions under which your product was tentatively approved...”

The Applicant did not provide the safety update (requested in the November 2, 2012 tentative approval letter) in their September 1, 2015 request for final approval. The Information Requests and the Applicant's Responses are summarized below.

Information Request #1 and Applicant's Response

Information Request #1: The Applicant was requested to submit the safety update requested in the November 2, 2012 tentative approval letter to the NDA. The Applicant was also requested to include a 4-month safety update report according to 21 CFR 314.50(d)(5)(vi)(b).

Applicant's Response to Information Request #1: The Applicant's response included the following statements:

- “...no new Safety Information was identified for Palonosetron between January 2012 until present in the FDA Adverse Event Reporting System (AERS) and the company's safety databases.”
- “A literature search was also conducted to identify articles published between January 2012 to February 2016. During the review of the available literature, we did not identify any new / significant safety information that would have an impact on the labeling or safety profile of Palonosetron.”

Information Request #2 and Applicant's Response

Information Request #2: The Applicant was requested to clarify the criteria they used to define “significant safety information” in the statement “During the review of the available literature, we did not identify any new / significant safety information that would have an impact on the labeling or safety profile of Palonosetron.” (see Applicant’s Response to Information Request #1 above)

Applicant’s Response to Information Request #2: The Applicant’s response stated the criteria used to define “significant safety information” in the literature search, and a description of each of the adverse effects identified. See below.

- Criteria Used to Define “Significant Safety Information”: The following criteria were used to define “significant safety information” in the literature search:
 - Not already listed in the most current Prescribing Information for approved Palonosetron injection and
 - Were of a serious nature (Grade 3 to 5) as described in the CTCAE (Common Terminology Criteria for Adverse Events)
 - Resulted in death
 - Were life-threatening
 - Required in patient hospitalization or prolongation of existing hospitalization
 - Resulted in persistent or significant disability or incapacity
 - Was a congenital anomaly or birth defect
 - Was an important medical event(s) that may not have been immediately life-threatening or resulted in death or hospitalization but that may have jeopardized the patient or required intervention to prevent one of the above outcomes.
- Adverse Effects Identified in the Literature Search: The literature search returned references to three serious adverse effects, namely seizures, QTc prolongation, and anaphylaxis. The Applicant noted that all three were already found to be listed as adverse effects in the Applicant’s proposed labeling submitted for Palonosetron injection, and were part of the reference drug Aloxi labeling. The Applicant noted that the remaining non-significant adverse effects found in the literature search were of a mild or moderate nature and were also part of the reference drug Aloxi labeling.

Discussion/Conclusion:

The approved Aloxi labeling was used as a guide to assess and revise the label for the new product proposed in the 505(b)(2) NDA. This reviewer concludes that no new safety findings should be incorporated in labeling. It should be noted that any palonosetron safety issues that have been addressed by the review division in the interim period between the tentative approval date and the resubmission and placed in the Aloxi label were also incorporated in the product label for Palonosetron Hydrochloride. Most notably, 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).

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/s/

ANIL K RAJPAL
02/29/2016

Summary Review for Regulatory Action

Date	November 2, 2012
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA	203050
Applicant Name	Dr. Reddy's Laboratories Ltd.
Date of Submission	January 3, 2012
PDUFA Goal Date	November 3, 2012
Established (USAN) Name	Palonosetron hydrochloride injection
Dosage Forms / Strength	Solution/ 0.25 mg/5 mL and 0.075 mg/1.5 mL in single (b) (4) vials
Proposed Indication(s)	<ol style="list-style-type: none"> 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. Postoperative nausea and vomiting (PONV) for up to 24 hours following surgery.
Action:	<i>Tentative Approval</i>

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Karyn Berry, MD/Ruyi He, MD
Pharmacology Toxicology Review	B. Emmanuel Akinshola, Ph.D./ Sushanta Chakder, Ph.D.
CMC Review	Bogdan Kurtyka, Ph.D./Moo Jhong Rhee, Ph.D.
Product Quality Microbiology	Steven P Donald, MS/Stephen Langille, PhD
Biopharmaceutics Review ONDQA	Mark Seggel, Ph.D./Angelica Dorantes, Ph.D.
Clinical Pharmacology Review	Kristina Estes, PharmD./Sue-Chih Lee, Ph.D.
DDMAC	Kathleen Klemm/Kendra Jones
CDTL Review	Marie Kowblansky, PhD
OSE/Office of Medication Error Prevention and Risk Management	Denise Baugh, PharmD, BCPS./Scott Dallas, RPh

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

CDTL=Cross-Discipline Team Leader

ONDQA = Office of New Drug Quality Assessment

Division Director Summary Review

1. Introduction

In this 505(b)(2) application, Dr. Reddy's Laboratories, Ltd. proposes a new palonosetron product for intravenous administration. The applicant references the Agency's previous findings of safety and efficacy for the palonosetron (Aloxi) NDA 021732. The reference product, Aloxi, is currently marketed in the US for intravenous administration in the same product presentations and for the same indications (listed on the cover page of this review) that the current NDA proposes. The product proposed for marketing by the applicant doesn't contain EDTA and has an acetate (b)(4). The amount of EDTA in Aloxi is (b)(4) mg/mL. (b)(4) NDA ineligible for review in Office of Generic Drugs, so it was submitted to CDER under 505(b)(2).

Like Aloxi, the product will be marketed in single (b)(4) doses, palonosetron 0.25 mg/5 mL and 0.075mg /1.5 mL. The actual vial sizes (container size) are 5 mL and 2 mL. CMC reviewers clarified, in post review communications, that the vial sizes for the proposed product and the reference product (b)(4) despite Aloxi labels available on DailyMed that suggest the smaller Aloxi vial is a 1.5 mL vial instead of a 2 mL vial (container size).

Although an oral formulation of Aloxi was also previously approved for marketing, it has never been marketed in the U.S.

(b)(4)

All reviewers have recommended approval of this NDA pursuant to section 505(b)(2); however, this NDA can only receive tentative approval at this time because the listed drug upon which this NDA relies is subject to a period of patent protection. Furthermore, the listed drug application holder has initiated a patent infringement suit against the applicant, Dr. Reddy's Laboratories Ltd. This review summarizes the high level findings and recommendations of the reviewers. Please refer to the CDTL review for a more detailed summary.

2. Background

This is a 505(b)(2) application. The applicant requested a biowaiver, which was granted by the Biopharmaceutics reviewers (see below). The minor differences between the proposed product and the reference product are not expected to impact safety or efficacy. No clinical trials were submitted for review. Palonosetron is one of a number of 5HT3 receptor antagonists approved for use as an antiemetic. See CDTL and Clinical reviews for information on the members and clinical features of this drug class.

3. CMC/Device

I concur with the conclusions reached by the CMC reviewers that this NDA has provided sufficient CMC information to assure identity, strength, purity, and quality of the drug product. The Office of Compliance has issued an overall recommendation of “Acceptable” for the facilities involved in the manufacture of the proposed product. The Office of Pharmaceutical Science Microbiology reviewer found the sterile process validation information for the product manufacturing, the container/closure integrity data, and the endotoxin and sterility testing procedures acceptable. He recommended approval. Labeling issues identified as approval issues in the CMC reviewer’s initial review have been satisfactorily addressed, as documented in his addendum review. A major review issue - a significant increase in an unidentified impurity during stability studies - was also adequately addressed by the applicant in response to information requests. The applicant’s investigation determined that the presence of the unidentified impurity in the affected batch was related to defective stoppers. They found that the (b)(4) protective coating on the stopper was not uniformly distributed. The applicant plans to change to a new stopper manufacturer; however, the CMC reviewers agreed that the stability data support a (b)(4) month expiration for the product with the current stoppers. Even the affected batch had acceptably (b)(4) the unidentified impurity at (b)(4) months, which supports use of the current stoppers with this expiration limit. When the applicant changes the stoppers used in the manufacturing process, appropriate data supporting the change, with new proposed expiration dates, must be submitted for review in a supplement to the NDA.

4. Nonclinical Pharmacology/Toxicology

The applicant did not conduct new nonclinical studies. The nonclinical sections of the product label will be consistent with those sections in the referenced product label. The pharmacology/toxicology reviewer noted the four (b)(4) impurities identified in the manufacturing process: (b)(4) which were also discussed by the CMC reviewer. The levels of these impurities and the unidentified impurity were controlled at acceptable levels, based on ICH guidelines. He also observed that the potential residual solvents in the manufacturing process will be controlled at levels that do not exceed ICH limits. The nonclinical pharmacology/toxicology reviewers recommended approval, and I concur.

5. Clinical Pharmacology/Biopharmaceutics

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. The reviewers examined the proposed labeling submitted in the NDA and found that in the sections relevant to Clinical Pharmacology, the proposed label is identical to the label of the approved reference product. The applicant for the reference product, Aloxi, has conducted a thorough QT study, and those data are included in both the Aloxi label and the label proposed by Dr. Reddy’s Laboratories, Ltd.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The Clinical reviewers have recommended approval of this NDA and I concur. No clinical trials or clinical studies were submitted for review. The Clinical reviewers concurred that the differences between the proposed and reference product (buffer and presence/absence of EDTA) would not be expected to alter efficacy. The removal of EDTA from the new product does not raise a safety concern for the new product.

8. Safety

As stated above, there were no clinical trials/studies submitted for review. I concur with the granting of the biowaiver and I agree that the differences between the proposed and reference product do not raise safety concerns for the new product. There are no new safety issues associated with the reference product that should preclude the approval of this NDA.

9. Advisory Committee Meeting

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

10. Pediatrics

The product proposed in this 505(b)(2) NDA does not contain a new active ingredient and is not a new dosage form. No new indication is proposed and no new dosing regimen is proposed. There is no new route of administration associated with the new product. For these reasons, the Pediatric Research Equity Act (PREA) does not apply to this application. No pediatric studies will be required as a condition of approval

11. Other Relevant Regulatory Issues

Because there were no clinical studies/trials conducted in support of this NDA, there was no request sent to Division of Scientific Investigations (DSI) for inspections.

This is a 505(b)(2) application. The CDTL has summarized in her review the 4 unexpired patents listed in the Orange Book for the reference NDA 21372 product, Aloxi (palonosetron hydrochloride) Injection. The applicant for this NDA submitted a Paragraph III certification for one of the patents, which does not expire until April 13, 2015 (the earliest of the 4 patents to expire), certifying that it won't market the product until after expiration of that patent. The applicant also submitted Paragraph IV certifications for the remaining 3 patents, which all expire in 2024. In these certifications, Dr. Reddy's Laboratories states that the patents are invalid and unenforceable. The patent holder for one of the latter patents has filed a suit against Dr. Reddy's Laboratories for patent infringement (in May of this year).

CDER 505(b)(2) committee met to discuss this application on September 24, 2012 and recommended a tentative approval action due to the existing patent protection for the listed reference application and the patent infringement suit. The committee will need to clear the application again when the request to obtain final approval is submitted.

12. Labeling

The labeling recommendations of all reviewers, including the Office of Medication Error Prevention and Risk Management reviewers, were incorporated in the proposed label. Questions were raised about what appeared to be class labeling in the 5HT3 product labels regarding cross reactivity for hypersensitivity reactions among drugs in the class. The strength of evidence to support this was questioned and OSE was consulted. This review is ongoing, and it was agreed that the product could be approved with the language currently found in the reference product label. If at the review's completion, the reviewers determine that the language in the 5HT3 product labels should be modified, labeling changes will be undertaken in the 5HT3 class. The label for the current NDA will be reviewed again at the time that the tentative approval period ends. The applicant must submit an amendment 2 or 6 months prior to expiration of the existing patents (the timing depends on whether there is substantive information for FDA to review). In that submission, the applicant must request final approval, must send in a safety update and must identify any changes in the conditions which the tentative approval was granted (including updated labeling). See the tentative approval letter for details.

No proprietary name has been proposed by the applicant.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Tentative approval
- Risk Benefit Assessment – I concur with the reviewers that there are no new risk/benefit concerns raised by the proposed product in this 505(b)(2) application.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – Not applicable.
- Recommendation for other Postmarketing Requirements and Commitments
None.

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/s/

DONNA J GRIEBEL
11/02/2012

Cross-Discipline Team Leader Review

Date	October 18, 2012
From	Marie Kowblansky, Ph.D., CMC Lead CDER/ONDQA/Division II
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 203050
Applicant	Dr. Reddy's Laboratories Ltd.
Date of Submission	January 3, 2012
PDUFA Goal Date	November 3, 2012
Proprietary Name / Established (USAN) names	Palonosetron Hydrochloride Injection (palonosetron hydrochloride)
Dosage forms / Strength	Solution/ 0.25mg/5mL & 0.075mg/1.5mL in single (b) (4) vials (b) (4)
Proposed Indication(s)	<u>Adults</u> <ul style="list-style-type: none"> 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:	Tentative 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 Dr. Reddy's Laboratories.

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 reference listed drug (RLD). The proposed drug product has the same route of administration, dosage form, active ingredient, strengths, and indications as Aloxi®, and a very similar composition, as well. It differs from the RLD only in that it contains acetate (b) (4) instead of citrate (b) (4) and does not contain EDTA. (The RLD contains (b) (4) mg/ml of EDTA.) The absence of EDTA is not expected to affect the efficacy of this product.

In view of the similarities between the proposed and reference listed drugs, a biowaiver for conducting *in-vivo* bioequivalence studies was granted on the basis of 21 CFR 320.22 (b): a drug product's *in vivo* bioavailability or bioequivalence may be considered self evident. 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®. The majority of the submitted information relates to the chemistry and controls used in the manufacture of this product.

2. Background

Palonosetron is a 5-HT₃ receptor antagonist that functions as an antiemetic and antinauseant. 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 and 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 (b) (4), the composition and strength of the current product (b) (4) to the 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). (b) (4)

3. CMC

As noted in the introduction, the qualitative and quantitative composition of the current product (both strengths) is the same as the composition of the reference listed drug (b) (4). The product is manufactured (b) (4) involving the following operations: (b) (4)

All inactive ingredients in the formulation conform to USP/NF monograph requirements and the proposed container/closure system conforms to all USP recommendations. For information regarding the manufacture, control, and characterization of the palonosetron hydrochloride drug substance, Dr. Reddy's Laboratories references DMF 23590, which has been reviewed and the DMF-holder has been found to be an acceptable source of drug substance for use in this product.

The product specification will include testing for appearance, identification, clarity, pH, assay (HPLC), identified and unidentified impurities (b) (4) extractable volume, particulate contamination, bacterial endotoxins, and sterility. For both drug substance and drug product, impurity limits conform to ICH recommendations. All tests and acceptance criteria are considered to be appropriate and sufficient for this type of product, assuring its identity, strength, quality and purity.

Steven P. Donald, M.S., the OPS Microbiology reviewer, has evaluated the sterile process validation information that was submitted, as well as Container/Closure integrity data and endotoxin and sterility testing procedures; all were judged to be acceptable and approval of this NDA was recommended from the Microbiology perspective.

Stability studies, which were conducted in both packaging configurations for the purpose of expiration dating the product, showed a significant increase in one of the unidentified impurities

(identified only by chromatographic retention time). Although this increase was observed in only one out of the six batches of product being studied, it appeared at both storage conditions, accelerated (40°C) and room temperature (25°C). At FDA's request the company conducted an investigation of this anomalous behavior and demonstrated that the batch of stoppers used in the manufacture of this stability batch were defective. Specifically, the (b) (4) protective coating was not uniformly distributed on the stopper surface (b) (4). Based on these findings, the applicant is planning to change to a new stopper manufacturer for this product in the future, but is not making this request at the present time because sufficient stability data with the new stoppers is currently unavailable. Instead, the company is seeking approval of this NDA with the current stopper, but requesting only a (b) (4) month expiration dating period. From our perspective, the stability data support a (b) (4) month expiry for the product, even after taking into account the batch with the defective stoppers; the higher levels of the unidentified impurity discussed above, are still within specification limits in all cases after (b) (4) months of storage.

An overall recommendation of "Acceptable" has been issued by the Office of Compliance for all facilities involved in manufacture of this product.

There are no unresolved CMC issues and the CMC reviewer, Dr. Bogdan Kurtyka, has recommended Approval of this NDA from the CMC perspective, with a (b) (4) month expiration dating period for the product.

4. Nonclinical Pharmacology/Toxicology

Dr. B. Emmanuel Akinshola, the nonclinical pharmacology/toxicology reviewer, has concluded that from a nonclinical pharmacology standpoint, the 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.

Since the sponsor did not submit any new nonclinical studies on palonosetron hydrochloride for this 505(b)(2) application, the nonclinical sections of the labeling are adopted from the innovator's labeling of Aloxi® Injection (NDA 021372). Consequently, no changes to the proposed labeling are recommended.

5. Clinical Pharmacology/ Biopharmaceutics

Dr. Kristina Estes, the Clinical Pharmacology reviewer has judged this application to be acceptable for approval from the viewpoint of the Office of Clinical Pharmacology. According to her review, "EDTA does not contribute to the efficacy of palonosetron and the absence (b) (4) in the proposed product is not expected to alter the efficacy of intravenous palonosetron." The proposed labeling is also acceptable with regard to clinical pharmacology; it is identical to the current Aloxi® label.

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.

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 RLD. 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)
The availability of Dr. Reddy's product would provide an alternative formulation, an EDTA-free formulation, of the product for the same indications as ALOXI®.

Dr Karyn Berry, the clinical reviewer recommends approval of this application for the same indications and target populations as ALOXI® Injection. No post-market risk evaluation and/or mitigation are recommended.

8. Safety

Palonosetron is a drug with widespread distribution and, according to the medical review, has a generally good safety profile. However, there exists the serious risk of cardiac arrhythmias, such as QTc prolongation, and reported risks of hypersensitivity reactions with the class of 5-HT3 receptor antagonists. Cardiac events are primarily documented with intravenous administration of these drugs. In December 2010, the FDA contraindicated the use of dolasetron I.V. in adults and children for the prevention of CINV due to serious cardiac arrhythmias, i.e. prolonged QTc interval. On June 29, 2012, the FDA issued a drug safety communication for Ondansetron (Zofran) I.V. related to QT prolongation observed at the 32 mg single I.V. administered dose.

Aloxi®, however, did not show significant QT prolongation and the package insert was modified in 2007 to include this information.

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.

Palonosetron Hydrochloride Injection does not contain a new active ingredient, new indications, new dosage forms, new dosing regimens, or new routes of administration compared to ALOXI, the RLD. Therefore, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the sponsor is not required to evaluate the use of Palonosetron Hydrochloride injection in the pediatric population.

11. Other Relevant Regulatory Issues

The reference listed application, NDA 21372 ALOXI® (palonosetron hydrochloride) Injection, has 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

Dr. Reddy's has submitted a Paragraph III certification [per 21 CFR 314.50(i)(1)(i)(A)(3)] for US Patent No. 5,202,333. As the patent does not expire until April 13, 2015, Dr. Reddy's certifies that they will not market their Palonosetron Injection product prior to expiration of this patent.

Dr. Reddy's has also submitted Paragraph IV certifications [per 21 CFR 314.50(i)(1)(i)(A)(4)] regarding the three additional patents, stating that they are invalid, unenforceable, and will not be infringed by the manufacture, use, or sale of Dr. Reddy's Palonosetron Hydrochloride Injection, which is the subject of this application.

On May 11, 2012, the patent holder filed a suit against Dr. Reddy's laboratories for infringement of patent 7,947,724.

12. Labeling

Kathleen Klemm from the Office of Prescription Drug Promotion (OPDP) and Kendra Y. Jones from the Division of Consumer Drug Promotion (DCDP) noted in her review that the proposed PI and PPI for palonosetron are 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 and concurs with the submitted labeling.

The Division of Medication Errors Prevention Analysis (DMEPA) evaluated the proposed container and carton labels and package insert for areas of vulnerability that could lead to medication errors. In Denise Baugh's, October 1, 2012 review, DMEPA recommended that the proposed label and labeling be improved by increasing the readability and prominence of important information to promote the safe use of this product and mitigate any confusion. (See the review.) All recommended changes have been made, as well as changes recommended by the CMC reviewer.

The Medical Reviewer, as well as the Clinical Pharmacology and Toxicology Reviewers have noted that the labeling is adopted from the innovator's labeling of Aloxi®. All three disciplines concur that no changes to the proposed labeling is required.

A consult has been requested from OSE to re-evaluate postmarketing reports of hypersensitivity and anaphylaxis associated with palonosetron hydrochloride injection and to evaluate the risk of cross reactivity reactions within the 5-HT3 class. Their review, which may include class labeling changes, will be completed after the approval date.

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

Cross Discipline Team Leader Review

Hydrochloride Injection would provide an alternative formulation that contains the same amount of the active ingredient as the ALOXI® product, but without EDTA.

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 this application. However, due to the unexpired patents for Aloxi®, a tentative approval is recommended at the present time, with the earliest possible approval date being April 13, 2015, when US Patent No. 5,202,333 expires.

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/s/

MARIE KOWBLANSKY
10/31/2012

CLINICAL REVIEW

Application Type NDA
Application Number(s) 203050
Priority or Standard Standard

Submit Date(s) 03 January 2012
Received Date(s) 03 January 2012
PDUFA Goal Date 03 November 2012
Division / Office DGIEP/ODE III

Reviewer Name(s) Karyn L. Berry, MD, MPH
Review Completion Date 17 October 2012

Established Name Palonosetron Hydrochloride injection
(Proposed) Trade Name Palonosetron Hydrochloride injection
Therapeutic Class 5-HT3 receptor antagonist
Applicant Dr. Reddy's Laboratories, Inc.

Formulation(s) Intravenous
Dosing Regimen 0.075 mg/1.5 mL and 0.25 mg/5 mL

Indication(s) Chemotherapy-Induced Nausea and Vomiting (0.25mg/5mL)

- 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

Postoperative Nausea and Vomiting (0.075mg/1.5mL)

- The prevention of post-operative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

Intended Population(s) Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

The sponsor, Dr. Reddy's Laboratories, Inc. submitted a 505(b)(2) application to support their product Palonosetron Hydrochloride Injection for the following 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
- the prevention of postoperative nausea and vomiting (PONV) for up to 24hours following surgery.

The applicant references the Agency's previous findings of safety and efficacy of ALOXI Injection (NDA 21372). The route of administration, indication and dosage of Dr. Reddy's formulation are the same as that of ALOXI®, the RLD. The applicant did not conduct and/or submit clinical trials for this submission.

The composition of ALOXI, the referenced listed drug (RLD), and Palonosetron Hydrochloride Injection (b) (4)

The ALOXI® formulation contains citrate buffer (b) (4) whereas Dr. Reddy's has replaced this (b) (4) with Sodium Acetate Trihydrate. Dr. Reddy's formulation does not contain disodium edentate (EDTA) (b) (4) while the ALOXI formulation contains EDTA. Due to the absence of EDTA in the proposed product, the application could not be submitted as a 505(j); therefore, the application has been filed under 505(b)(2) referencing intravenous ALOXI.

In this 505(b)(2) NDA submission, the Applicant requested a waiver of the *in vivo* bioequivalence study requirement as allowed under 21 CFR 320.22(b)(1)(i) and (ii). The Biopharmaceutics reviewer noted that the proposed drug has the same concentration of active ingredient and the same dosage form, route of administration and indication as the RLD. The only difference between the two drug formulations is that the proposed new drug product contains sodium acetate rather than sodium citrate (b) (4) and it does not contain EDTA. Based on this data, the Biopharmaceutics Division granted the biowaiver.

1.1 Recommendation on Regulatory Action

As per the Chemistry reviewer, the data demonstrates that the proposed drug, Palonosetron Hydrochloride Injection, is equivalent to ALOXI Injection in terms of quality and stability. Therefore, this reviewer recommends tentative approval of the applicant's drug Palonosetron Hydrochloride Injection 0.075 mg/1.5 mL and 0.25 mg/5 mL for the

same indications and target populations as ALOXI Injection. Tentative approval is based on the applicant's statement that they will not market their product until the innovator's current patent expires on April 13, 2015

1.2 Risk Benefit Assessment

Palonosetron Hydrochloride Injection has been marketed in the US since 2003 under the tradename ALOXI® Injection. The proposed new formulation provides the equivalent amount of the active ingredient as ALOXI Injection, the RLD. The availability of Dr. Reddy's product, Palonosetron Hydrochloride would provide an additional formulation that does not contain [REDACTED] (b) (4) EDTA, for the prevention of CINV and PONV. This new formulation provides the equivalent amount of the active ingredient as ALOXI, the RLD.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and/or mitigation are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements and/or commitments are recommended. Palonosetron Hydrochloride Injection does not contain a new active ingredient, new indications, new dosage forms, new dosing regimens, or new routes of administration compared to ALOXI, the RLD. Therefore, as per the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the sponsor is not required to evaluate the use of Palonosetron Hydrochloride injection in the pediatric population for the same indications as adults.

2 Introduction and Regulatory Background

Consideration was given to whether this application should most appropriately be reviewed by Office of Generic Drugs as a 505(j) application; however, the Agency reviewed information provided by the applicant regarding the product and manufacturing process and determined that a 505(b)(2) application would be appropriate.

The reference listed application, NDA 21372 ALOXI (palonosetron hydrochloride) injection, has four unexpired patents listed in the Orange Book:

- 5202333 – for prevention of chemotherapy-induced nausea and vomiting (expires April 13, 2015)
- 7947724
- 7947725
- 7960424

With their NDA, Dr. Reddy's submitted a Paragraph III certification [per 21 CFR 314.50(i)(1)(i)(A)(3)] for 5202333. As this patent does not expire until April 13, 2015, Dr. Reddy's noted that they will not market their Palonosetron Hydrochloride Injection until this patent expires.

Dr. Reddy's submitted Paragraph IV certifications [per 21 CFR 314.50(i)(1)(i)(A)(4)] against the other three listed patents noting that they are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Dr. Reddy's palonosetron hydrochloride injection for which the NDA was submitted. Dr. Reddy's was sued for patent infringement by the patent holder on May 11, 2012 for patent 7947724.

Palonosetron Hydrochloride Injection is a 5-HT₃ receptor antagonist. It is an antiemetic/antinauseant drug. NDA 203050 for Palonosetron Hydrochloride Injection, 0.075mg/1.5mL and 0.25mg/5mL refers to the listed drug, ALOXI® (Palonosetron Hydrochloride) Injection, 0.075mg/1.5mL and 0.25mg/5mL (NDA 21372) published in Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book). The active ingredient, route of administration, dosage form and strength of Dr. Reddy's Laboratories Limited's Palonosetron Hydrochloride Injection, 0.075mg/1.5mL and 0.25mg/5mL are the same as that of Helsinn Healthcare's Aloxi® (Palonosetron Hydrochloride) Injection, 0.075mg/1.5mL and 0.25mg/5mL.

The difference between the two drug formulations [REDACTED] (b) (4)
[REDACTED] The ALOXI formulation contains citrate buffer [REDACTED] (b) (4)
[REDACTED] whereas the applicant has replaced this [REDACTED] (b) (4) with Sodium Acetate Trihydrate. The applicant's drug formulation does not contain disodium edentate (EDTA) [REDACTED] (b) (4) while the ALOXI formulation contains EDTA.

[REDACTED] (b) (4)

Dr. Reddy's Laboratories (DRL) has developed a palonosetron formulation which is free of disodium edetate [REDACTED] (b) (4)

[REDACTED]

(b) (4)
 (b) (4)
 The applicant states that the formulation does not affect the efficacy of palonosetron, which works exclusively via antagonism of the 5-HT₃ receptor.

Table 1: Side by side comparison of information demonstrating that the proposed product is the same as the listed product

	Proposed Drug Dr Reddy's Palonosetron Hydrochloride Injection,	Listed Drug – Helsinn Healthcare Aloxi®
Conditions of use:	<p>1.1 Chemotherapy-Induced Nausea and Vomiting (0.25mg/5ml) Palonosetron hydrochloride injection is indicated for:</p> <ul style="list-style-type: none"> 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 <p>1.2 Postoperative Nausea and Vomiting (0.075mg/1.5ml) Palonosetron hydrochloride injection is indicated for:</p> <ul style="list-style-type: none"> The prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated. <p>As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period, Palonosetron hydrochloride injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.</p>	<p>1.1 Chemotherapy-Induced Nausea and Vomiting (0.25mg/5ml) ALOXI is indicated for:</p> <ul style="list-style-type: none"> 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 <p>1.2 Postoperative Nausea and Vomiting (0.075mg/1.5ml) ALOXI is indicated for:</p> <ul style="list-style-type: none"> The prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated. <p>As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period, ALOXI is recommended even where the incidence of postoperative nausea and/or vomiting is low.</p>
Active	Palonosetron Hydrochloride	Palonosetron Hydrochloride

	Proposed Drug Dr Reddy's Palonosetron Hydrochloride Injection,	Listed Drug – Helsinn Healthcare Aloxi®
ingredient(s)		
Dosage Form:	Palonosetron hydrochloride injection is supplied as a single-use sterile, clear, colorless solution in glass vials	ALOXI is supplied as a single-use sterile, clear, colorless solution in glass vials
Route of Administration:	Intravenous Injection	Intravenous Injection
Strengths:	<ul style="list-style-type: none"> • 0.25 mg (free base) /5 ml • 0.075 mg (free base) /1.5 ml. 	<ul style="list-style-type: none"> • 0.25 mg (free base)/5 ml • 0.075 mg (free base) /1.5 ml.

Applicant's table, Module 1 - 1.12.12 Comparison of generic drug and referenced drug

2.1 Product Information

Proposed Trade Name: Palonosetron Hydrochloride Injection

Proposed Indication:

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

Proposed Dosage Forms and Strengths: 0.075 mg/1.5 mL and 0.25 mg/5 mL

Proposed Age Group: Adults

Pharmacologic Class: Serotonin 5-HT₃ receptor antagonist

Route of administration, description and formulation: An off white to white crystalline powder; administered intravenously and available as a 5 ml single (b)(4) vial or a 1.5 ml single (b)(4) vial. Each 5 ml vial contains 0.25 mg palonosetron base as hydrochloride,

Proposed treatment regimen:

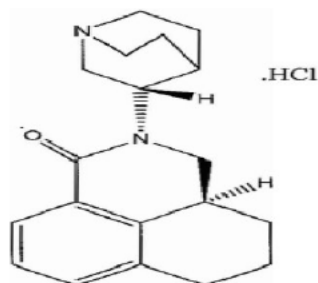
Chemotherapy-Induced Nausea and Vomiting

- Adult Dosage: a single 0.25 mg intravenous dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy.

Postoperative Nausea and Vomiting

- Adult Dosage: a single 0.075 mg intravenous dose administered over 10 seconds immediately before the induction of anesthesia.

Structural formula:



2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2: Currently Available Prescription Products for the Proposed Indications

DRUG NAME Formulations (Sponsor)	Approval Date	Indications and Dosages*
5-HT₃ Receptor Antagonists		
ZOFRAN® (ondansetron) Oral tablets Orally disintegrating tablets Oral solution Intravenous injection (GlaxoSmithKline)	1991	<p>Adults CINV – 16mg IV x 1 or 0.15mg/kg IV q4 hrs. x 3 CINV-HEC -- 24mg oral x 1 day CINV-MEC – 8mg oral BID x 2-3 days PONV— 4mg IV; 16mg oral 1 hr prior to induction RINV – 8mg oral TID x 1-3 days</p> <p>Pediatrics CINV – for ≥6 mo., 0.15-mg/kg IV q4 hrs. x 3 CINV-MEC – for 6mo. to 18yrs, 0.15mg/kg IV q4 hrs x 3; for ≥12 y.o., same oral as adult; 4-11y.o., 4mg oral TID x 2-3 days PONV—IV only, 1 month to 12 y.o. – a single 0.1-mg/kg dose for patients weighing ≤ 40 kg, or a single 4-mg dose for patients weighing > 40 kg RINV – N/A</p>
ANZEMET (dolasetron mesylate) Oral tablet Oral solution Intravenous injection (Aventis Pharmaceuticals)	1997	<p>Adults CINV--100mg oral x 1 PONV – 12.5mg IV x 1; 100mg oral x 1 RINV– N/A</p> <p>Pediatrics CINV – for 2 y.o. and older, 1.8mg/kg oral x 1 PONV– for 2 y.o. and older, 0.35mg/kg IV x 1; 1.2mg/kg oral x1 RINV – N/A</p>

DRUG NAME Formulations (Sponsor)	Approval Date	Indications and Dosages*
KYTRIL (granisetron) Oral tablet Oral solution Intravenous injection (Roche Pharmaceuticals)	1993	<p>Adults CINV- 10mcg/kg IV on the days chemotherapy is given; 2mg oral on the days chemotherapy is given PONV – 1mg IV x 1 RINV– 2mg oral x 1</p> <p>Pediatrics CINV – IV same as adults for 2 y.o. and older PONV– N/A RINV– N/A</p>
ALOXI (palonosetron HCl) Oral capsule Intravenous injection (MGI Pharma)	2003	<p>Adults CINV-HEC (acute)– 0.25mg IV x 1 CINV-MEC (acute & delayed) – 0.25mg IV x 1; 0.5mg oral x 1 capsule PONV – 0.075mg IV x 1</p> <p><u>No Approved Pediatric Indications</u></p>
SANCUSO (transdermal granisetron) (ProStrakan)	2008	<p>Adults CINV-HEC CINV-MEC Single patch is applied to upper outer arm 24 hrs before chemo; patch is removed 24 hrs after chemo; patch can be worn for up to 7 days</p> <p><u>No Approved Pediatric Indications</u></p>
H1 Receptor Antagonists		
Hydroxyzine hydrochloride oral capsule oral suspension intramuscular injection (Generic) <i>Note: oral syrups and tablets are available but approved for indications other than antiemesis.</i>	1957	<p>Adults NV -- 25–100 mg IM Pre- and Postoperative adjunctive medication -- 25–100 mg IM RINV – N/A</p> <p>Pediatrics NV-- 0.5 mg/lb body weight IM Pre- and Postoperative adjunctive medication -- 0.5 mg/lb body weight IM RINV – N/A</p>
NK1 Receptor Antagonists		

DRUG NAME Formulations (Sponsor)	Approval Date	Indications and Dosages*
EMEND (aprepitant/fosaprepitant dimeglumine) Oral capsule Intravenous injection (Merck)	2003	<p>Adults CINV-HEC – 125mg PO or 115mg IV on Day 1; 80mg PO on Days 2 & 3 CINV-MEC – 125mg PO or 115mg IV on Day 1; 80mg PO on Days 2 & 3 PONV – 40mg IV x 1</p> <p><i>No Approved Pediatric Indications</i></p>

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, palonosetron, was first approved on July 25, 2003 in ALOXI® Injection. Palonosetron is currently marketed in the US as the ALOXI® brand. Palonosetron hydrochloride is available in injectable form for intravenous administration. The oral formulation, ALOXI capsules (NDA-22233), was approved on August 22, 2008 for the prevention of CINV in acute MEC in adults. However, the oral formulation has never been marketed in the US.

In this NDA application, Dr. Reddy's Lab, Inc. submits Palonosetron Hydrochloride injection as an alternative formulation to the referenced ALOXI injection product.

2.4 Important Safety Issues With Consideration to Related Drugs

Palonosetron is a drug with widespread distribution and a generally good safety profile. However, there exists the serious risk of cardiac arrhythmias, such as QTc prolongation, and reported risks of hypersensitivity reactions with the class of 5-HT₃ receptor antagonists.

Cardiac events have been primarily documented with intravenous administration of these drugs. In December 2010, the FDA contraindicated the use of dolasetron I.V. in adults and children for the prevention of CINV due to serious cardiac arrhythmias, i.e. prolonged QTc interval. On June 29, 2012, the FDA issued a drug safety communication for Ondansetron (Zofran) I.V. related to QT prolongation observed at the 32 mg single I.V. administered dose.

The ALOXI sponsor conducted and submitted a thorough QT trial in 2007. No significant effect of palonosetron administration on any ECG interval including QTc duration at doses up to 2.25 mg QT interval was detected in this trial. ALOXI has an effect on the QT interval but it is small. The ALOXI package insert was revised to include this data.

Hypersensitivity reaction risks are currently labeled in the Contraindications and Warnings/Precautions sections.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

N/A

2.6 Other Relevant Background Information

N/A

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the overall submission was good. It was well-organized, with appropriately placed links to allow easy navigation throughout the application.

3.2 Compliance with Good Clinical Practices

N/A

3.3 Financial Disclosures

No clinical trials were conducted for this 505(b)(2) application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Per the review of the CMC reviewer, the applicant of this NDA provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The office of Compliance issued an overall recommendation of “Acceptable” for the facilities involved in this application. The CMC reviewer has identified labeling deficiencies that should be addressed prior to approval. These include:

- Section 11 (Description) of package insert does not list quantitative amount sodium acetate, as required for injectable dosage forms.
- For the established name in the labels, “palonosetron” and “hydrochloride” should

be in the same line on container and carton labels, as follows:
 Palonosetron Hydrochloride Injection.
 0.075 mg/1.5 mL and 0.25 mg/5 mL

See the CMC review by Bogdan Kurtyka for full details.

A biowaiver was granted by ONDQA for the in vivo bioequivalence study based on the similarities between the reference drug and the proposed product. See full review by M. Seggel.

Table 3: Comparative Qualitative and Quantitative Formula

Qualitative and Quantitative composition of Aloxi® (Helsinn Healthcare)			Qualitative and Quantitative composition of Palonosetron Hydrochloride injection (Dr. Reddy's Laboratories)		
Ingredient	Function	Qty (mg/mL)	Ingredient	Function	Qty (mg/mL)
Palonosetron Hydrochloride	Active Pharmaceutical ingredient	(b) (4)	Palonosetron Hydrochloride	Active Pharmaceutical ingredient	(b) (4)
Mannitol		(b) (4)	Mannitol (b) (4) USP		(b) (4)
Edetate disodium (b) (4)					
citrate (b) (4)			Sodium acetate trihydrate USP		
Water for Injection			Water for Injection USP	Vehicle	q.s. to 1.0 mL
Sodium Hydroxide	For adjustment pH	q.s to adjust the pH of 4.5 to 5.5	Sodium Hydroxide USNF	For adjustment pH	q.s to adjust the pH of 4.5 to 5.5
Hydrochloric acid	For adjustment pH	q.s to adjust the pH of 4.5 to 5.5	Hydrochloric acid USNF	For adjustment pH	q.s to adjust the pH of 4.5 to 5.5

* (b) (4) Palonosetron Hydrochloride is equivalent to 0.05 mg of Palonosetron base.

q.s – quantity sufficient.

Applicant's table: Module 2 - 2.3 Quality overall summary

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

No new toxicology studies were submitted under NDA 203050, but per the Pharmacology/Toxicology reviewer, the toxicology studies conducted by the innovator have established the safety of palonosetron hydrochloride. See the review by B. Emmanuel Akinshola for additional details.

4.4 Clinical Pharmacology

The application was found acceptable by the Office of Clinical Pharmacology. The Clinical Pharmacology reviewer also found the proposed labeling to be acceptable in regards to clinical pharmacology. See the review by K. Estes for additional details.

4.4.1 Mechanism of Action

As per the Aloxi package insert

4.4.2 Pharmacodynamics

As per the Aloxi package insert

4.4.3 Pharmacokinetics

As per the Aloxi package insert

5 Sources of Clinical Data

No clinical trials were submitted in this 505(b)(2) application.

5.1 Tables of Studies/Clinical Trials

N/A

5.2 Review Strategy

5.3 Discussion of Individual Studies/Clinical Trials

Not applicable

6 Review of Efficacy

Efficacy Summary

6.1 Indication

6.1.1 Methods

N/A

6.1.2 Demographics

N/A

6.1.3 Subject Disposition

N/A

6.1.4 Analysis of Primary Endpoint(s)

N/A

6.1.5 Analysis of Secondary Endpoints(s)

N/A

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

N/A

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

N/A

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

N/A

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

N/A

7.1.2 Categorization of Adverse Events

N/A

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

N/A

7.2.2 Explorations for Dose Response

N/A

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

N/A

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

N/A

7.3 Major Safety Results

7.3.1 Deaths

N/A

7.3.2 Nonfatal Serious Adverse Events

N/A

7.3.3 Dropouts and/or Discontinuations

N/A

7.3.4 Significant Adverse Events

N/A

7.3.5 Submission Specific Primary Safety Concerns

N/A

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

N/A

7.4.2 Laboratory Findings

N/A

7.4.3 Vital Signs

N/A

7.4.4 Electrocardiograms (ECGs)

N/A

7.4.5 Special Safety Studies/Clinical Trials

N/A

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

N/A

7.5.3 Drug-Demographic Interactions

N/A

7.5.4 Drug-Disease Interactions

N/A

7.5.5 Drug-Drug Interactions

N/A

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

N/A

7.6.2 Human Reproduction and Pregnancy Data

N/A

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant requested a waiver of pediatric assessment requirements for all pediatric age groups, in accordance with section 505B (a)(4)(A)(iii) of the Act. The applicant's rationale was that Palonosetron failed 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.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Since this application does not meet any of the criteria for PREA, the applicant is not required to submit an assessment for pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

N/A

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

9 Appendices

9.1 Literature Review/References

9.2 Labeling Recommendations

Labeling negotiations with the Applicant are ongoing.

A consult was requested from the Division of Medication Errors Prevention Analysis (DMEPA) to evaluate the proposed container label, carton and insert labeling for Palonosetron Injection (NDA 203050) for areas of vulnerability that could lead to medication errors. DMEPA concluded that the proposed label and labeling could be improved to increase the readability and prominence of important information to promote the safe use of the product and mitigate any confusion. See the review by Denise Baugh, October 1, 2012 for specific recommendations.

A consult was requested from the Office of Surveillance and Epidemiology (OSE) to re-evaluate postmarketing reports of hypersensitivity and anaphylaxis associated with palonosetron hydrochloride injection and to evaluate the risk of cross reactivity reactions within the 5-HT₃ class. A review was conducted by OSE in June 2005 to assess hypersensitivity with palonosetron and the recommendation at the time by OSE was to update the label to reflect postmarketing reports of hypersensitivity and rarely anaphylaxis. The review by OSE, which may include class labeling changes, will be completed after the approval date.

A consult was requested from the Division of Medical Policy Programs (DMPP) to review the applicant's proposed Patient Package Insert (PPI) for palonosetron hydrochloride injection. The following were their recommended changes for the PPI:

- simplify wording and clarified concepts where possible
- ensure that the PPI is consistent with the Prescribing Information (PI)
- remove unnecessary or redundant information
- ensure that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Medical Reviewer's comments: The proposed labeling is adopted from the innovator's labeling of Aloxi (NDA 21372). Therefore, other than changes recommended by DMEPA and DMPP, no additional changes in the proposed labeling are recommended. Once

Clinical Review
Karyn L. Berry, MD, MPH
NDA 203050
Palonosetron Hydrochloride Injection

the OSE consult is completed, any recommended labeling changes will be reviewed at that time.

9.3 Advisory Committee Meeting

N/A

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

/s/

KARYN L BERRY
10/22/2012

RUYI HE
10/22/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203050

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

Stamp Date: January 3, 2012

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

NDA/BLA Type: Standard

On initial overview of the NDA/BLA application for filing:

This is a 505 (b)(2) new drug application that refers to the listed drug, Aloxi® (Palonosetron Hydrochloride) Injection manufactured by Helsinn Healthcare, the holder of the approved application (NDA#021372). The sponsor reports that the qualitative and quantitative composition of their product (Palonosetron Hydrochloride Injection, 0.075mg/1.5mL and 0.25mg/5mL) is the same as the composition of reference listed drug Aloxi® (Palonosetron Hydrochloride Injection, 0.075mg/1.5mL and 0.25mg/5mL) manufactured by Helsinn Healthcare, (b) (4)

The sponsor did not conduct Clinical or Clinical Pharm studies.

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?			X	
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?			X	
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				This is a 505(b)(2) application
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?			X	No dose ranging trials were conducted

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The applicant has submitted waiver requests for pediatric trials
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	No clinical trials were conducted
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	No clinical trials were conducted
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
38.	Has the applicant submitted the required Financial Disclosure information?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Reviewing Medical Officer

Date

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

KARYN L BERRY
03/01/2012

RUYI HE
03/02/2012