CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203050Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 203050	Submission Date(s): 09/01/2015
Brand Name	TBD
Generic Name	Palonosetron Hydrochloride Injection
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Dr. Reddy's Laboratories
Submission Type; Code	Amendment- Request for final approval
Formulation; Strength(s)	Solution for intravenous administration 0.075 mg/1.5 mL and 0.25 mg/5 mL
Indications	MEC- Prevention of acute and delayed CINV HEC- Prevention of acute and delayed CINV Prevention of post-operative nausea and vomiting

Executive Summary

NDA 203050, Palonosetron Hydrochloride Injection is acceptable from a Clinical Pharmacology perspective.

The original 505 b(2) NDA submission referencing Aloxi® received a tentative approval from the agency on 11/02/2012. Clinical Pharmacology review in this regard also found the original NDA submission to be acceptable, as noted by Dr. Estes and Dr. Lee in their review in DARRTs dated 10/02/2012.

On September 01, 2015 the sponsor submitted an amendment to the NDA titled- 'Request for final approval'. In this regard, the proposed drug product labeling has been reviewed by DCP3 and modifications were proposed to make it consistent with the PLR format. Please see the final approved labeling in DARRTs once it becomes available.

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

/s/

SANDHYA K APPARAJU
02/08/2016

SUE CHIH H LEE
02/09/2016

Clinical Pharmacology Review

NDA: **203050**	Submission Date: 3 JAN 2012
Submission Type; Code:	Original Submission
Brand/Code Name:	Palonosetron Hydrochloride Injection
Generic Name:	Palonosetron Hydrochloride Injection
Primary Reviewer:	Kristina Estes, Pharm.D.
Secondary Reviewer	Sue Chih Lee, Ph.D.
OCP Division:	Division of Clinical Pharmacology III
OND Division:	Division of Gastroenterology and Inborn Errors Products
Sponsor:	Dr. Reddy's Laboratories
Formulation; Strength(s):	Palonosetron for Injection; 0.075 mg/1.5 mL and 0.25 mg/5 mL
Approved Indications:	• Prevention of Acute and Delayed HEC • Prevention of Acute and Delayed MEC • Postoperative Nausea and Vomiting

Background

Intravenous palonosetron (Aloxi®) is a 5-HT_3 receptor antagonist approved in 2003 and is marketed by Helsinn Healthcare in the US. It is indicated 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 the prevention of postoperative nausea and vomiting for up to 24 hours following surgery. An oral formulation of Aloxi® is also currently marketed by Helsinn.

Dr. Reddy's Laboratories developed an intravenous formulation of palonosetron that contains sodium acetate (b) (4). In addition, the proposed product does not contain EDTA (b) (4) which is present in the innovator product (see Table 1 on page 2). (b) (4) 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®. The concentration of EDTA in Aloxi® is (b) (4). EDTA does not contribute to the efficacy of palonosetron (b) (4) in the proposed product is not expected to alter the efficacy of intravenous palonosetron. Therefore, the sponsor intends to rely on previous findings of efficacy and safety of Aloxi® for approval of their proposed product.

Recommendation

The application is acceptable from the viewpoint of the Office of Clinical Pharmacology. The proposed labeling is also acceptable and is identical to the current Aloxi® label with regard to clinical pharmacology.

Additional Information

The table below shows the difference in the composition of the reference drug (Aloxi®) and the proposed palonosetron injection.

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		
(b) (4)					
Water for Injection			Water for Injection USP	Vehicle	q.s. to 1.0 mL
Sodium Hydroxide	For pH adjustment	q.s to adjust the pH of 4.5 to 5.5	Sodium Hydroxide USNF	For pH adjustment	q.s to adjust the pH of 4.5 to 5.5
Hydrochloric acid	For pH adjustment	q.s to adjust the pH of 4.5 to 5.5	Hydrochloric acid USNF	For pH adjustment	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.

A biowaiver was granted by ONDQA (see review by Dr. Seggel in DAARTS dated 21 JUN 2012) for the in vivo bioequivalence study based on the similarities between the reference drug and the proposed product. Please also refer to reviews by Dr. Kurtyka (CMC) dated 10 AUG 2012 and Dr. Akinshola (pharm/tox) dated 13 SEP 2012 for additional information supporting approval of the proposed product.

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

/s/

KRISTINA E ESTES
10/01/2012

SUE CHIH H LEE
10/02/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203-050	**Reviewer:** Mark R. Seggel	
Submission Date:	03-JAN-2012 (eCTD 0000)		
Division:	DGIEP	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Dr. Reddy's Laboratories		
Trade Name:	-	**Date Assigned:**	04-JAN-2012
Generic Name:	Palonosetron HCl	**Date of Review:**	15-FEB-2012
Indication:	Prevention of CINV and PONV	**Type of Submission:**	505(b)(2) NDA;
Formulation / strengths	0.075 mg* / 1.5 mL; 0.25 mg* / 5 mL (b) (4)	**GRMP Goal:**	-
Route of Administration	Intravenous Injection	**PDUFA Goal:**	03-NOV-2012
Type of Review	Biowaiver Request		

SUMMARY:

Palonosetron hydrochloride is an antiemetic / antinauseant indicated for the prevention of acute and delayed nausea, vomiting associated with Chemotherapy (CINV), and Postoperative Nausea and Vomiting (PONV) for up to 24 hours following surgery. It is currently available as Aloxi® under NDA 21-372. Aloxi® Injection is a sterile, clear, colorless, non-pyrogenic, isotonic, buffered solution for intravenous administration. Aloxi Injection is supplied as a 5 mL single use vial or a 1.5 mL single use vial. Each 5 m1 vial contains the equivalent of 0.25 mg palonosetron base as the hydrochloride and each 1.5 mL vial contains the equivalent of 0.075 mg palonosetron base as the hydrochloride.

The product proposed by Dr. Reddy's Laboratories differs from the RLD in that it contains sodium acetate rather than sodium citrate (b) (4) and it does not contain disodium edetate (EDTA; (b) (4) The Applicant claims that EDTA is not required in their formulation (b) (4)
Based on the similarities between the RLD and proposed new drug product (same strength, (b) (4) same pH), Dr. Reddy's Laboratories has requested a biowaiver pursuant to 21 CFR 320.22(b)(1) [eCTD section 1.12.15].
It is noted that there are no significant new impurities in the proposed product. Although no clinical pharmacology or clinical studies were conducted in support of the new product, the clinical review team has not identified any new safety concerns.

REVIEW:

The Biopharmaceutics review is focused on the evaluation and acceptability of the data supporting the biowaiver request.

RECOMMENDATION:

A waiver of the *in vivo* bioequivalence study requirement is granted. From the Biopharmaceutics perspective, NDA 203-050 for Palonosetron HCl Injection is recommended for approval.

Signature	**Signature**
Mark R. Seggel Biopharmaceutics Reviewer Office of New Drug Quality Assessment	Angelica Dorantes, Ph.D. Biopharmaceutics Team Leader Office of New Drug Quality Assessment

BIOPHARMACEUTICS ASSESSMENT

Evaluation of Biowaiver Request

In this 505(b)(2) NDA submission, the Applicant is requesting a waiver of the *in vivo* bioequivalence study requirement as allowed under 21 CFR 320.22(b)(1)(i) and (ii). The comparative pharmaceutical information for the proposed Palonosetron HCl Injection product and the RLD product is as follows:

Qualitative and Quantitative Comparative Of Composition
Dr. Reddy' Formulation Vs Aloxi®

Qualitative and Quantitative composition of Aloxi®			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 ingredient	(b) (4)	Palonosetron Hydrochloride	Active ingredient	(b) (4)
Mannitol		(b) (4)	Mannitol USP		(b) (4)
Edetate disodium (b) (4)					
(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 pH adjustment	q.s to adjust the pH of 4.5 to 5.5	Sodium Hydroxide USNF	For pH adjustment	q.s to adjust the pH of 4.5 to 5.5
Hydrochloric acid	For pH adjustment	q.s to adjust the pH of 4.5 to 5.5	Hydrochloric acid USNF	For pH adjustment	q.s to adjust the pH of 4.5 to 5.5

* (b) (4) Palonosetron hydrochloride is equivalent to 0.05 mg of Palonosetron
q.s – quantity sufficient

Reference Listed Drug:

Active Ingredient:	PALONOSETRON HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; INTRAVENOUS
Proprietary Name:	ALOXI
Applicant:	HELSINN HLTHCARE
Strength:	EQ 0.25MG BASE/5ML (EQ 0.05MG BASE/ML)
Application Number:	N021372
Product Number:	001
Approval Date:	Jul 25, 2003
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	PALONOSETRON HYDROCHLORIDE
Dosage Form;Route:	INJECTABLE; INTRAVENOUS
Proprietary Name:	ALOXI
Applicant:	HELSINN HLTHCARE
Strength:	EQ 0.075MG BASE/1.5ML (EQ 0.05MG BASE/ML)
Application Number:	N021372
Product Number:	002
Approval Date:	Feb 29, 2008
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:

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

Reviewer's Assessment:

The proposed drug product is a parenteral solution for administration by injection. The proposed drug product has the same concentration of active ingredient and differs from the RLD in that it contains sodium acetate rather than sodium citrate (b) (4) and it does not contain EDTA. It has the same dosage form, route of administration and indication as the RLD. Therefore, 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.

####

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

/s/

MARK R SEGGEL
06/21/2012

ANGELICA DORANTES
06/21/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**203050**	**Brand Name**	**Not Provided**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Palonosetron Hydrochloride**
Medical Division	**DGIEP**	**Drug Class**	**Antiemetic (5-HT$_3$ antagonist)**
OCP Reviewer	**Kris Estes**	**Indication(s)**	**CINV**
OCP Team Leader	**Sue Chih Lee**	**Dosage Form**	**Injection**
Pharmacometrics Reviewer		**Dosing Regimen**	**0.25 mg or 0.075 mg one time**
Date of Submission	**3 January 2012**	**Route of Administration**	**IV**
Estimated Due Date of OCP Review		**Sponsor**	**Dr. Reddy's Laboratories**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**3 November 2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**0**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions,			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	submitted in the appropriate format (e.g., CDISC)?				
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes.

If the NDA/BLA is not fileable from the clinical pharmacology 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.

Kristina Estes — 2 March 2012

Reviewing Clinical Pharmacologist — Date

Sue Chih Lee — 5 March 2012

Team Leader/Supervisor — Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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

/s/

KRISTINA E ESTES
03/02/2012

SUE CHIH H LEE
03/07/2012