CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207963Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 207963	Submission Date(s): 09/15/2015
Brand Name	TBD
Generic Name	Palonosetron HCl
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Exela Pharma Services
Submission Type; Code	Resubmission; 505b(2); Standard Review
Formulation; Strength(s)	0.25 mg per 2 mL solution for injection
Indication	Chemotherapy induced nausea and vomiting, CINV (b) (4)

1 Executive Summary

1.1 Recommendation

NDA 207963 (resubmission) is acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Sponsor is seeking approval of their proposed palonosetron HCl intravenous injection, 0.25 mg per 2 mL for CINV (b) (4) indications in adults. This is a 505 b(2) application using Aloxi I.V. as the reference formulation. The original NDA was received by the agency on August 7, 2014 and accepted on August 15.

There was no new clinical pharmacology information in the original NDA and therefore after reviewing the proposed labeling and make revisions which were accepted by the sponsor at the time, OCP had no approvability issues (see review in DARRTs dated May 12, 2015).

A biowaiver request was included in the NDA as per 21 CFR §320.22(a) and was reviewed by ONDQA- Biopharmaceutics group. This waiver was not granted in the original cycle due to pending safety concerns from the clinical discipline. Sponsor received a complete response letter on June 15, 2015 citing safety, product quality and regulatory issues.

This class 2 resubmission was submitted on September 15, 2015 addressing the deficiencies listed in the complete response letter. There was no new clinical pharmacology information in the resubmission. Labeling was reviewed and minor revisions were proposed to align it better with the PLR format and to remove redundancies. Please see the final approved labeling once available.

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/s/

SANDHYA K APPARAJU
02/23/2016

SUE CHIH H LEE
02/23/2016

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 207963	Submission Date(s):08/07/2014 (received); 08/15/2014 (accepted)
Brand Name	TBD
Generic Name	Palonosetron HCl
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Sue Chih Lee, Ph.D.
OCP Division	DCP3
OND Division	DGIEP
Sponsor	Exela Pharma Sciences
Submission Type	Original; 505b(2); Standard Review
Formulation; Strength(s)	0.25 mg per 2 mL solution for injection
Adult Indication	Chemotherapy induced nausea and vomiting, CINV (b) (4)

1 Executive Summary

1.1 Recommendation

NDA 207963 is acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Sponsor is seeking approval of their proposed palonosetron HCl intravenous injection, 0.25 mg per 2 mL for CINV (b) (4) indications in adults. This is a 505b(2) application using Aloxi I.V. as the reference formulation. A biowaiver request has been included in the NDA as per 21 CFR §320.22(a) and was reviewed by ONDQA- Biopharmaceutics group. A local irritation clinical trial has been submitted which was reviewed by clinical discipline. There is no new clinical pharmacology information. The proposed labeling has been reviewed by DCP3 and modifications were proposed to make it consistent with the PLR format and accepted by the sponsor. Please see the final labeling once available.

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/s/

SANDHYA K APPARAJU
05/11/2015

SUE CHIH H LEE
05/12/2015

BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 207963	**Reviewer:** Vidula R. Kolhatkar, Ph.D.	
Submission Date:	August 08, 2014, and March 11 and March 12, 2015		
Division:	Division of Gastroenterology and Inborn Errors Products	**Quality Assessment Lead:** Tien-Mien Chen, Ph.D.	
Applicant:	Exela Pharma Services	**Acting Supervisor:** Tapash Ghosh, Ph.D.	
Trade Name:	Palonosetron hydrochloride injection, 0.125 mg/mL	**Date Assigned:**	December 22, 2014
Established Name:	Palonosetron hydrochloride Injection	**Date of Review:**	May 2, 2015
Indication:	Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy	**Type of Submission:** 505(b)(2) NDA	
Formulation/ strengths	Sterile injectable solution, 0.125 mg/mL		
Route of Administration	Intravenous injection		
Type of Review:	Biowaiver Request		

SUMMARY:

Background: Palonosetron is indicated for prevention of nausea and vomiting after/during moderately and highly emetogenic cancer chemotherapy treatments. (b) (4) (b) (4) Aloxi (Palonosetron HCl) IV (Intravenous injection) under NDA 21372 was approved 07/25/03.

Submission: On August 08, 2014, Exela Pharma Services submitted a 505(b)(2) new drug application for Palonosetron HCl Injection referencing Aloxi as the RLD (reference listed drug). The applicant requested a biowaiver for Palonosetron Hydrochloride Injection based on 21 CFR § 320.22(b).

The applicant was requested to provide a table of side-by-side comparison for the formulations between the proposed drug product and the reference product and to provide justification demonstrating that 1) Any differences in osmolality and in pH values and 2) The absence of mannitol in the proposed product does not impact the bioavailability of the drug in previous information requests sent to the Applicant.
The Agency sent another request to provide more biowaiver information demonstrating that the PK profile data of the proposed and RLD products would be similar despite the differences in the inactive ingredients on February 24, 2015. The applicant responded on March 11 and March 12, 2015.

Reviewer's Comment: Biopharmaceutics review is focused on the evaluation of the requested information to support the biowaiver request. The Division of Biopharmaceutics is in agreement with the Medical Division's decision for the concerns on the differences in osmolality between the Applicant's proposed drug product and the RLD.

RECOMMENDATION:

From the Biopharmaceutics perspective, the proposed biowaiver request could not be granted since the proposed drug product and RLD are considered different in osmolality Therefore, NDA 207963 could not be recommended for approval.

Signature

Vidula R. Kolhatkar -S

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Date: 2015.05.11 17:12:50 -04'00'

Vidula R. Kolhatkar, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Signature

Tienmien Chen -A

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Date: 2015.05.11 17:57:50 -04'00'

Tien-Mien Chen, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

cc. TGhosh; PSeo

Assessment of Biopharmaceutics information

- The applicant provided a side-by-side table comparing the proposed product and the RLD.

Table 1. Side-by-side comparison of the RLD and the proposed drug product

Exela's Formulation		Helsinn Healthcare SA Formulation[1]	
Ingredients	Composition	Ingredients	Composition
Palonosetron Hydrochloride	0.125 mg/mL (as base)	Palonosetron Hydrochloride	0.25 mg/5 mL (as base) or 0.075 mg/1.5 mL (as base)
Mannitol	Absent	Mannitol	(b) (4)
Disodium edetate	Absent	Disodium edetate	
Citrate buffer	Absent	Citrate buffer	
			(b) (4)
Water for Injection, USP	q.s.	Water for Injection, USP	q.s.

[1]Information regarding Helsinn Healthcare SA, ALOXI® (Palonosetron Hydrochloride) Injection formulation was obtained from the current package insert, vial label, and carton

- The proposed product does not contain buffer and tonicity agent. In the pre-IND meeting for this application (IND 116583) the applicant was recommended to perform a local irritation study in healthy volunteers to address potential safety concerns. (please refer to meeting comments communicated to the applicant on November 30, 2012)
- The applicant amended the NDA on December 31, 2014 to update the composition. The applicant modified the composition (b) (4) Final composition of the proposed drug product is displayed in the following table.

Table 2. Final composition of the proposed drug product

Component	Quality Standard	Function	Palonosetron Hydrochloride Injection (0.125 mg/mL, as base)
Palonosetron Hydrochloride	N/A	Drug Substance	0.125 mg/mL (as base)
Water for Injection	USP	Solvent	q.s. to 2.0 mL

- The applicant requested biowaiver per 21 CFR § 320.22(b). Following comments were included in the 74 day letter by the biopharmaceutics reviewer Dr. Kareen Riviere:
  1. *Provide the proposed drug product's and listed drug product's osmolality and pH values and the analytical procedure/s used to measure them.*
  2. *Provide justification demonstrating that the absence of mannitol in the proposed product does not impact the bioavailability of the drug.*

- Following Information request was sent to the applicant on February 24, 2015
  You have not provided adequate biowaiver information demonstrating that the PK

profile data of your proposed and reference listed drug products would be similar despite the differences in the inactive ingredients. To support the approval of the biowaiver, submit a justification and evidence that the absence of disodium edetate and citrate buffer and the differences, if any, in pH and osmolality do not affect the pharmacokinetics of your proposed drug product compared to that of the reference drug product. You may use literature references to support your justification.

You are reminded to respond to the previous information request (October 27, 2014) on 1) the osmolality, pH values, and the analytical procedure/s used to measure them and 2) a justification for the absence of mannitol for your proposed drug product.

- The applicant responded on March 11 and March 12, 2015.

- The applicant provided a table of side-by-side comparison of formulations between the listed drug (Aloxi) and the proposed drug product (Table 3). This includes data from the proposed product, three lots of pH adjusted batches XLNC1306, XLNC1307, XLNC1308 (Manufactured March 2013) and one lot of pH unadjusted product XLNB1421 (Manufactured February 2014), and one lot of the reference product Aloxi injection Lot Number 34002929 (Expiration Date 05/19). The applicant is seeking approval for pH unadjusted product. Comparison of pH and osmolality of the proposed product and the reference product are reported in the following table.

Table 3. Comparative data between RLD and the proposed drug product

Lot Number	pH	Osmolality
XLNC1306	(b) (4)	
XLNC1307		
XLNC1308		
XLNB1421		
RLD – 34002929		
RLD – 34002929		

- To support the difference in the pH the applicant has cites clinical trial data of palonosetron hydrochloride published in Europe. It is stated that in Phase I and II trials were conducted with the formulation (b) (4) Despite the differences between the two formulations, a bridging BE study between the Phase I/II and Phase III formulations was not required by the EMA and bioequivalence of these two formulations was considered to be self-evident because both formulations were administered as aqueous solutions by IV route, and for the same duration (i.e., over 30 seconds), and the differences in excipients did not seem to affect bioavailability.

- Based on a reference cited, the applicant has stated that the total blood buffer value is 76.8 mEq/L for a change of one pH unit. The proposed drug product has only palonosetron hydrochloride and water for injection and does not contain a buffer or any pH adjusters does not affect the blood buffer or blood pH upon introduction into systemic circulation. Based on the buffer capacity of blood and total volume of administration, this is considered acceptable.

- The proposed product does not contain any tonicity agent. The osmolality was measured to be 0 mOsm/Kg vs. about 300 mOsm/Kg for the reference product (using mannitol as the tonicity agent). This reviewer calculated the osmolality based on the concentration of palonosetron hydrochloride to be close to zero. This was confirmed with the CMC reviewers. The proposed product is therefore, hypotonic with zero measured osmolality and it is stated that a total volume of 2 mL of the proposed product will have negligible, if any, effect on blood osmolality. The applicant conducted a safety study in healthy volunteers to evaluate safety of the product. This study is reviewed by medical officer Dr. Laurie Muldowney. The medical division has concerns on the differences in osmolality between the proposed drug product and the RLD.

- The reference product in addition to mannitol also contains disodium edetate [redacted] (b) (4) and citrate buffer.

- [redacted] (b) (4) Bioequivalence was considered self-evident and BE study was not considered necessary. This is reasonable. Phase II formulation that did not contain EDTA and was one of the important efficacy studies. The applicant cited another reference EDTA did not affect pharmacokinetic profile of parentally administered drug propofol. Overall, applicant's argument that disodium edetate does not alter the pharmacokinetics or bioavailability of palonosetron hydrochloride injection is considered acceptable.

Recommendation

From the Biopharmaceutics perspective, the proposed biowaiver request could not be granted since the proposed drug product and RLD are considered different in osmolality for which the Medical Division has concerns. Therefore, NDA 207963 could not be recommended for approval.