CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208109Orig1s000

PRODUCT QUALITY REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Products			
Application No.:	NDA 208109	**Primary Reviewer:** Vincent (Peng) Duan, Ph.D. **Acting Quality Assessment Lead:** Tien Mien Chen, Ph.D.	
Submission Date:	6/30/2017		
Applicant:	Fresenius Kabi USA		
Trade Name:	Palonosetron Hydrochloride Injection, 0.25 mg/5 mL	**Date Assigned:**	08/17/2017
Generic Name:	Palonosetron Hydrochloride Injection	**Date of Review:**	09/11/2017
Indication:	Indicated for prevention of acute and delayed nausea and vomiting associated with the initial and repeated courses of moderately and highly emetogenic cancer chemotherapy. It is also indicated for prevention of postoperative nausea and vomiting for up to 24 hours following surgery.	**Type of Submission:** Request for final approval	
Formulation/strengths:	Injection/0.25 mg/5 mL		
Route of Administration:	i.v.		

Background:
NDA 208109 Palonosetron Hydrochloride Injection, 0.25 mg/5 mL was tentatively approved On 7/29/16, because of an ongoing patent infringement lawsuit. In the tentative approval letter, the Agency instructed the Applicant to submit an amendment two to six months prior to the date that this NDA will be eligible for approval. On 6/30/17, Fresenius Kabi submitted a request for final approval stating their subject lawsuit has been dismissed. Additionally, in the submission the applicant submitted a CMC amendment and safety update.

Submission: The followings summarize the changes and updates the Applicant submitted in this CMC amendment:

CHEMISTRY, MANUFACTURING AND CONTROLS UPDATES

Please find the following updates to Fresenius Kabi USA, LLC's (FK USA) tentatively approved NDA for Palonosetron HCl Injection.

DRUG SUBSTANCE

Since the USP monograph for Palonosetron HCl has become official on August 1, 2016, FK USA has revised the drug substance specifications, test method validations and reference standards to be in compliance with the USP monograph. The following drug substance sections of the NDA have been revised accordingly:

Section	Revision / Justification
3.2.S.3 DS Characterization of Impurities	Updated to add Impurities nomenclature per the USP monograph. Two new potential impurities added to match the DS DMF.
3.2.S.4.1 DS Specifications	Added/revised tests to align with USP monograph.
3.2.S.4.2 DS Analytical Procedures	Section revised to include USP tests and their compendial method references. No new non-compendial analytical procedures added.
3.2.S.4.3 DS validation of Analytical Procedures	Added: Assay/Impurities USP Method Verification Report; Assay Impurities Equivalency Report – USP vs FRD110; Reference Standards Equivalency Report USP vs FK.
3.2.S.4.5 DS Justification of Specifications	Updated to address changes due to USP monograph.
3.2.S.5 DS Reference Standards	Added USP reference standards used for Assay/Impurities method verification.

DRUG PRODUCT

The following drug product sections have minor revisions as summarized below:

Section	Revision / Justification
3.2.P.5.1 DP Specifications	Created separate tables for vials and prefilled syringes for clarity. Minor updates to the limits for pH, Volume Check/Extractable Volume, and Assay to harmonize the proposed release and stability limits to a single limit based on consistent stability results throughout shelf life.
3.2.P.5.6 DP Justification of Specifications	Justification provided to support the proposed limits.

SAFETY UPDATE

As recommended in the tentative approval letter, FK USA is providing literature based non-clinical and clinical safety update along with the safety data analysis from the FAERS database for Palonosetron in the SECTION 2.7.4 Clinical Safety for the period 17 May 2016 (from the last update) to 2 June 2017.

Review: Biopharmaceutics review in last cycle of NDA 208109 submission evaluated the biowaiver request submitted by the Applicant, and the biowaiver request was acceptable based on review from Dr. Duan dated 02/01/2016. In the current CMC amendment, since there is no new data or changes related with Biopharmaceutics, additional Biopharmaceutics review is not necessary.

Recommendation: There is no change related to Biopharmaceutics perspective in this CMC amendment. From Biopharmaceutics perspective, NDA 208109 is recommended for final approval.

Signature

Vincent (Peng) Duan, Ph.D.
Biopharmaceutics Reviewer
Office of new Drug Products

Signature

Tien Mien Chen, Ph.D.
Biopharmaceutics Quality Assessment Lead
Office of New Drug Products

I concur. 10/09//17

Acting Biopharm Lead.
DBBII/ONDP/OPQ

cc. TGhosh; PSeo

Peng Duan

Digitally signed by Peng Duan
Date: 10/10/2017 09:23:30AM
GUID: 54579633000330547a76e69866efb4b3

Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 10/30/2017 11:26:03AM
GUID: 508da7230002a2433ddcef616ca190df

FACILITIES

IQA Review Guide Reference

Product Background: Palonosetron Hydrochloride Injection, is intended for the for moderately emetogenic cancer chemotherapy to prevent acute and delayed nausea and vomiting associated with initial and repeat courses in adults. Vial and Pre-filled syringe presentations are proposed.

NDA: 208109-ORIG-1-RESUB-22

Drug Product Name / Strength: Palonosetron Hydrochloride Injection, 0.25 mg/5 mL

Route of Administration: Intravenous Injection

Applicant Name: Fresenius Kabi USA, LLC

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: *The facilities supporting the NDA were acceptable in the previous review cycle (ORIG-1-RESUB-19 project) and continue to be acceptable in the current review cycle. No new facility information is noted in the Resubmission*

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Original/Resubmission/Class 1	06/10/2016

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

List Number of Comparability Protocols (ANDA only): Not applicable.

3.2.S.2 Manufacture

Summary of Facility Information:

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Vidya Pai

Digitally signed by Vidya Pai
Date: 10/27/2017 06:49:04AM
GUID: 53b581d20000464509a65e37ec9ad4a2

Juandria Williams

Digitally signed by Juandria Williams
Date: 10/27/2017 08:20:47AM
GUID: 513b65ab0005b7cb48614cd3d341d717

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **October 23, 2017**

From: **Hamid Shafiei, Ph.D.**
Drug Product Reviewer, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 208109**

Subject: **Review of the Resubmission Requesting the Full Approval of the New Drug Application Tentatively Approved on July 29, 2016**

This 505(b)(2) new drug application for palonosetron hydrochloride injection, 0.25mg/5mL (free base) supplied in a glass vial or in a prefilled syringe was reviewed and recommended for approval from the drug product and label/labeling perspective on 03/24/2016. This application was also recommended for approval from all OPQ review disciplines on April 26, 2016 (refer to IQA for the overall quality assessment, but it was tentatively approved by the Agency.

The applicant has submitted an amendment, resubmission/class 2, to the application on June 30, 2017 requesting full approval of this application. This amendment also includes minor changes to the acceptance criteria in the drug product specification. The proposed changes include minor changes to the acceptance limits for pH, volume check/extractable volume, and assay. The changes are suggested to harmonize the release specification with the shelf-life specification (regulatory specification). Additionally, for clarification the applicant has separated the regulatory specifications for the drug product packaged in the glass vials container and prefilled syringes. The drug product specification submitted in the original application and the regulatory specifications for the drug product packaged in the glass vials and prefilled syringes submitted in this amendment are provided in Table 1 through Table 3, respectively. Th applicant has also provided the statement that the finished drug product complies t (b) (4) in the updated specification section of this amendment (3.2.P.5.1). The applicant has submitted updated justification for specification that include appropriate rationale for the proposed changes.

Table 1: Drug product specification submitted in the original submission

Test	Acceptance Criteria	Test Method[1]
Description	Clear, colorless solution	Visual inspection
Clarity	Clear	EP 2.2.1 USP <1>
Color	Not more colored than (b) (4)	EP 2.2.2. USP <1>
Particulate contamination - Subvisible particles ≥ 10 µm	NMT 6,000 per container	EP 2.9.19 USP <788>
Particulate contamination - Subvisible particles ≥ 25 µm	NMT 600 per container	EP 2.9.19 USP <788>
Visible particles	Essentially free from visible particles	EP 2.9.20 USP <1>
pH	Release: (b) (4) Shelf life: (b) (4)	EP 2.2.3 USP <791>
Volume check	(b) (4)	EP 2.9.17 USP <1>
Identification:		
A: HPLC	The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the Assay and ratio (R) of the retention times is: (b) (4) ≤ R ≤ (b) (4)	HPLC In-house method
B: UV	(b) (4)	HPLC In-house method
Assay:		
Palonosetron	(b) (4)	HPLC In-house method
Purity:		
A: Any Other Individual Impurity	NMT (b) (4) %	HPLC In-house method
B: Total Impurities	NMT (b) (4) %	HPLC In-house method
Bacterial Endotoxins	NMT (b) (4) EU/mL	USP <85>
Sterility	sterile	USP <71>

NMT : Not more than; NLT : Not less than

1 References to compendia signify current compendia. If a compendial monograph or test changes, Fresenius Kabi USA will implement the changes and report them via annual report.

Tests	Acceptance criteria	Method
Container Closure Integrity Testing[1]		
Blue Dye test	Conform	EP 3.2.9

1 CCIT is not a (b) (4) Please note that the Container/Closure Integrity test is performed at 12 and 24 months in accordance with the February 2008 Guidance for Industry: Container Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol of Sterile Products.

Table 2: Drug product regulatory specification provided in the resubmission for glass vials

Test	Acceptance Criteria	Test Method[1]
Description	Clear, colorless solution	Visual inspection
Clarity	Clear	EP 2.2.1 USP <1>
Color	Not more colored than (b) (4)	EP 2.2.2, USP <1>
Particulate contamination - Subvisible particles ≥ 10 µm	NMT 6,000 per container	EP 2.9.19 USP <788>
Particulate contamination - Subvisible particles ≥ 25 µm	NMT 600 per container	EP 2.9.19 USP <788>
Visible particles	Essentially free from visible particles	EP 2.9.20 USP <1>
pH	Release: (b) (4) Shelf life: 4.5 – 5.5	EP 2.2.3 USP <791>
Volume check	Not less than nominal volume of (b) (4) mL	EP 2.9.17 USP <1>
Identification:		
A. HPLC	A. The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the Assay and ratio (R) of the retention times is: (b) (4) ≤ R ≤ (b) (4)	A. HPLC In-house method
B. UV	B. (b) (4)	B. HPLC In-house method
Assay:		
Palonosetron	(b) (4) %	HPLC In-house method
Purity:		
A. Any Other Individual Impurity	A. NMT (b) (4) %	A. HPLC In-house method
B. Total Impurities	B. NMT (b) (4) %	B. HPLC In-house method
Bacterial Endotoxins	NMT (b) (4) EU/mL	USP <85>
Sterility	sterile	USP <71>

NMT : Not more than; NLT : Not less than

Tests	Acceptance criteria	Method
Container Closure Integrity Testing[1]		
Blue Dye test	Conform	EP 3.2.9

[1] CCIT is not a (b) (4) Please note that the Container/Closure Integrity test is performed at 12 and 24 months in accordance with the February 2008 Guidance for Industry: Container Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol of Sterile Products.

Table 3: Drug product regulatory specification provided in the resubmission for prefilled syringes

Test	Acceptance Criteria	Test Method[1]
Description	Clear, colorless solution	Visual inspection
Clarity	Clear	EP 2.2.1 USP <1>
Color	Not more colored than (b) (4)	EP 2.2.2, USP <1>
Particulate contamination - Subvisible particles ≥ 10 µm	NMT 6,000 per container	EP 2.9.19 USP <788>
Particulate contamination - Subvisible particles ≥ 25 µm	NMT 600 per container	EP 2.9.19 USP <788>
Visible particles	Essentially free from visible particles	EP 2.9.20 USP <1>
pH	Release: (b) (4) Shelf life: 4.5 – 5.5	EP 2.2.3 USP <791>
Volume check / Extractable Volume	Not less than nominal volume of (b) (4) mL. Not more than (b) (4) mL	EP 2.9.17 USP <1>
Identification:		
A. HPLC	A. The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the Assay and ratio (R) of the retention times is: (b) (4) ≤ R ≤ (b) (4)	A. HPLC In-house method
B. UV	B. (b) (4)	B. HPLC In-house method
Assay:		
Palonosetron	(b) (4) %	HPLC In-house method
Purity:		
A. Any Other Individual Impurity	A. NMT (b) (4) %	A. HPLC In-house method
B. Total Impurities	B. NMT (b) (4) %	B. HPLC In-house method
Bacterial Endotoxins	NMT (b) (4) EU/mL	USP <85>
Sterility	sterile	USP <71>
Syringe Tests:		
Break Loose Force / Static Friction	NMT (b) (4) N	S175
Gliding Force / Dynamic Friction	NMT (b) (4) N	S175

NMT : Not more than; NLT : Not less than

Tests	Acceptance Criteria	Method
Container Closure Integrity Testing[1]		
Blue Dye test	Conform	EP 3.2.9

[1] CCIT is not a (b) (4) Please note that the Container/Closure Integrity test is performed at 12 and 24 months in accordance with the February 2008 Guidance for Industry: Container Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol of Sterile Products.

Review Comments and Evaluation

Submission of two separate specifications for the glass vials and prefilled syringes certainly helps reduce confusion and allows the addition of prefilled syringe specific testing and acceptance criteria to the prefilled syringe specification.

The proposed change in the release acceptance limits for pH from (b) (4) (b) (4) t (b) (4) (b) (4) is acceptable since the proposed upper limit i (b) (4) than the original and the lower limit is harmonized with the limit in the shelf-life specification.

The proposed change in the release acceptance limits for assay from (b) (4)% (b) (4)% t (b) (4)% (b) (4)% to harmonized with shelf-life acceptance limits has no significant impacts on the drug product strength and is considered acceptable.

The change in the acceptance limits of volume check/extractable volume to NLT (b) (4)mL from originally proposed NLT (b) (4) and NMT (b) (4) is only proposed for the glass vials. No changes to acceptance limits of volume check/extractable volume for the prefilled syringes are proposed. The proposed volume check of NLT (b) (4)mL without and specific upper limit for glass vials is acceptable since the injection volume is drawn and measured using a syringe.

Recommendation:

Based on the ONDP assessment of the information provided in this amendment regarded as resubmission/class 2 does not impact the previous final recommendation of Approval made in the addendum dated April 25, 2016, to Review #1.

Hamid R. Shafiei, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Chief, Branch V, Division II, ONDP

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 10/23/2017 02:18:50PM
GUID: 507d824300005f344cf8b5e5989f0057

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 10/23/2017 02:20:45PM
GUID: 502d0913000029f9798ca689a802fa55

77MEMORANDUM

Date: 18-Sep-2017
From: Joseph Leginus, Ph.D., Review Chemist, Office of New Drug API
To: NDA 208109, Palonosetron Hydrochloride Injection
Subject: Drug Substance Approval Recommendation

NDA Background:

- On 29-Jun-2015, the Applicant, Fresenius Kabi USA LLC, submitted NDA 208109 for palonosetron hydrochloride injection. The Application received a Tentative Approval on 29-Jul-2016 due to an ongoing patent infringement lawsuit.
- On 30-Jun-2017, the Applicant submitted a request for final approval stating their subject lawsuit had been dismissed.

Original Submission Background:

- CMC information for the Palonosetron Hydrochloride drug substance was referenced to (b) (4) (reviewed as Adequate on 16-Mar-2016).
- A recommendation for Approval from the Drug Substance perspective was provided by B. Stevens (29-Feb-2016) contained within the 25-Jul-2016 Integrated Quality Assessment (IQA).
- In a 25-Apr-2016 Memo, Application Technical Lead (ATL) H. Shafiei recommended Approval from the OPQ perspective for NDA 208109 for Palonosetron Hydrochloride Injection.

Resubmission

- CMC information for the Palonosetron Hydrochloride drug substance continues to be referenced to (b) (4). Updates to DMF (b) (4) have been recently reviewed (5-Sep-2017 by J. Leginus) as Adequate.
- The 30-Jun-2017 NDA 208109 resubmission includes a CMC Amendment describing minor updates to comply with the recent introduction of a USP monograph for Palonosetron Hydrochloride.

Note: Since the time of the Tentative Approval of NDA 208109 (29-Jul-2016), a USP monograph for Palonosetron Hydrochloride was published and became official (1-Aug-2016). As a result, the Applicant has made revisions to the drug substance specifications, test method validations and reference standards to be in compliance with the USP monograph. The resubmission provides for changes/updates in the following sections in the NDA for Palonosetron Hydrochloride USP:

8 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Conclusion:
The Applicant has made acceptable revisions to the drug substance specifications, test method validations and reference standards to be in compliance with the USP monograph for Palonosetron Hydrochloride USP. There are no approvability issues for the drug substance portion of this application. There are no deficiencies that need to be reported to the Applicant with respect to the drug substance portion of this application. The data is adequate to support the use of Palonosetron Hydrochloride drug substance in the manufacture of Palonosetron Hydrochloride Injection drug product.

Joseph Leginus, PhD
Review Chemist

Donna Christner, PhD
Office of New Drug API, Chief (Acting), Branch II

Joseph Leginus

Digitally signed by Joseph Leginus
Date: 9/18/2017 09:27:33AM
GUID: 508da7230002a1c9abb2c3ae2ae521b9

Donna Christner

Digitally signed by Donna Christner
Date: 9/18/2017 02:09:53PM
GUID: 502d0913000029cd728469a6a8a14427

MEMORANDUM

DEPATMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTARTION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 25, 2016

FROM: Hamid R. Shafiei, Ph.D.
Review Chemist/ATL (Branch V/Division II/ONDP)

TO: Review #1 of NDA 208109 Emend for Oral Suspension

SUBJECT: Final OPQ Recommendation

In the Review # 1 (April 19, 2016) of NDA 208109 Palonosetron Hydrochloride Injection for intravenous administration, this NDA was not recommended for approval from the OPQ perspective due to the following reason:

- An overall recommendation of "Acceptable" from the Office of Process and Facilities regarding the facilities involved in this NDA was ***not*** yet issued

On April 22, 2016, the Office of Process and Facilities has made an overall recommendation of "Acceptable" for the facilities involved in this NDA (see the **Attachment 1**)

On April 22, 2016, the applicant submitted revised labels per FDA's recommendation for using "Single-Dose syringe" instead of "(b) (4)" (see the **Attachment 2**). This was based on the current naming convention proposed in the October 2015 draft guidance, "Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use: Guidance for Industry".

Recommendation:

This NDA is now recommended for **approval** from the OPQ perspective with the product expiation dating period of 24 months.

Application Technical Lead
Hamid R. Shafiei, Ph.D.
CMC Reviewer, Branch V, Division II, ONDP

Hamid Shafiei -S
Digitally signed by Hamid Shafiei -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hamid Shafiei -S, 0.9.2342.19200300.100.1.1=2000350820
Date: 2016.04.26 13:37:14 -04'00'

9 Page(s) have been Withheld in Full as b4 (CCI/TS) and Draft Labeling immediately following this page

Recommendation: This 505(b)(1) NDA is **not** recommended for **APPROVAL** in its present form per 21 CFR 314.125(b) (13) .

NDA 208109
Review 1

Drug Name/Dosage Form	Palonosetron Hydrochloride Injection
Strength	0.25 mg/5 mL (as free base)
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	Fresenius Kabi USA
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
NDA original Submission	06/29/2015	All
Amendment	10/02/2015	General correspondence
Amendment	10/16/2015	CDRH and Drug Product
Amendment	10/23/2015	CDRH and Drug Product
Amendment	11/10/2015	CDRH and Drug Product
Amendment	12/04/2015	Process and Facilities and Drug Product
Amendment	12/14/2015	Quality Microbiology and Drug Product
Amendment	01/27/2016	Drug Product
Amendment	02/10/2016	Quality Microbiology, Drug Product and Process and Facilities
Amendment	02/16/2016	Drug Product
Amendment	02/18/2016	Administrative
Amendment	02/29/2016	CDRH and Drug Product
Amendment	03/10/2016	Environmental Assessment

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ben Stevens	OMPT/CDER/OPQ/ONDP/DND API/NDBII
Drug Product	Hamid Shafiei	OMPT/CDER/OPQ/ONDP/DND PII/NDPBV
Process	Xueli Zhu	OMPT/CDER/OPQ/OPF/DPAIII/ PABVIII
Microbiology	Yuansha Chen	OMPT/CDER/OPQ/OPF/DMA/M ABII
Facility	Vipul Dholakia	OMPT/CDER/OPQ/OPF/DIA/IA BIII
Biopharmaceutics	Peng Duan	OMPT/CDER/OPQ/ONDP/DB/B BII
Regulatory Business Process Manager	Truong Quach	OMPT/CDER/OPQ/OPRO/DRBP MI/RBPMBI
Application Technical Lead	Hamid Shafiei	OMPT/CDER/OPQ/ONDP/DND PII/NDPBV
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue	OGROP/ORA/OO/OMPTO/DMP TPO/MDTP
Environmental Assessment (EA)	N/A	

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	Palonosetron Hydrochloride	1	1) 03/16/2015 by Dr. Q. Shi 2) 11/06/2015 by Dr. B. Stevens	Adequate
	Type III		Glass vials	N/A		
	Type III		Stoppers	N/A		
	Type III		(b) (4)	N/A		
	Type III		Syringe	N/A		

1 Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	NDA 21372	Reference Listed Drug: Aloxi (palonosetron hydrochloride) Injection

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	Completed	Complete Response	03/29/2016	Dr. Sapana Patel
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug substance and drug product.

All labels/labeling issued have been resolved.

However, the Office of Process and Facility has ***not*** made an overall "Approval" recommendation regarding the facilities involved in this NDA.

Therefore, from the OPQ perspective, this NDA is ***not*** ready for approval in its present form, per 21 CFR 314.125(b) (13).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

Palonosetron hydrochloride,

(*S*)-2-[(3*S*)-Quinuclidin-3-yl]-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*]isoquinolin-1-one hydrochloride

is the hydrochloride salt of palonosetron, an antiemetic and antinauseant agent. It is a serotonin-3 (5-HT_3) receptor antagonist with a strong binding affinity for this receptor. Palonosetron hydrochloride is a white to off-white non-hygroscopic crystalline powder with a melting point >290°C and a predicted pKa of 9.77 as free base. This API has two chiral centers and is produced (b) (4) (b) (4) It is freely soluble in water, very soluble in buffers with pH ranging from 1.2 to 7.5, and slightly soluble in ethanol and isopropanol. Based on the OGD 2010 palonosetron guidance, palonosetron hydrochloride can be classified as a BCS Class I API.

Full description of the (b) (4), manufacturing process and scale, manufacturing process controls, and release and stability testing of palonosetron hydrochloride intended for use as the API in this new drug application is provided in drug substance manufacturer, (b) (4) This DMF was recently reviewed by Dr. Qian Shi of DMF Team 7 on 03/16/2015 and found to be adequate. All additional submissions to this DMF since Dr. Shi's review, if any, have been assessed by the drug substance reviewer, Dr. Benjamin Stevens on 11/06/2015. Dr. Stevens has concluded that DMF (b) (4) remains **adequate** to support this new drug application.

In conclusion, the drug substance, palonosetron hydrochloride is produced by a well-established well-characterized robust manufacturing process with appropriate control strategies that enables production of API with consistent quality batch to batch. This API is tested against a specification that assures the identity, strength, purity, and quality of API at release and throughout the designated retest period. The stability data provided in the referenced DMF (b) (4) supports the proposed (b) (4) year retest period for this API.

B. Drug Product [Established Name] Quality Summary

Fresenius Kabi USA, LLC has submitted this new drug application under 505(b)(2) for Palonosetron Hydrochloride Injection, 0.28mg/5mL (0.056mg/mL) equivalent to 0.25mg/5mL (0.050mg/mL) palonosetron as free base, for intravenous use. Palonosetron hydrochloride, is hydrochloride salt of Palonosetron, an antiemetic and antinauseant agent. Palonosetron is a serotonin-3 (5-HT3) receptor antagonist with a strong binding affinity for this receptor. Palonosetron Hydrochloride Injection is a sterile drug product indicated for prevention of acute and delayed nausea and vomiting associated with the initial and repeated courses of moderately and highly emetogenic cancer chemotherapy. It is also indicated for prevention of postoperative nausea and vomiting for up to 24 hours following surgery. Palonosetron Hydrochloride Injection is to be marketed as a 5mL unit (0.25mg/5mL palonosetron as free base) in a (b) (4) Glass vial enclosed with a 20 mm, (b) (4) stopper and as a 5mL unit in a prefilled (b) (4) syringe with a (b) (4) rubber plunger and tip cap. To date, palonosetron hydrochloride injection drug products in pre-filled syringe presentation have not been approved for marketing in the United State. The currently approved Aloxi® (palonosetron hydrochloride) Injection has been referenced in this application as the reference listed drug (RLD).

Pharmaceutical/formulation development for this drug product was mainly focused on the development of a drug product with an identical quality target product profile (QTPP) as the currently marketed ALOXI®. The components in the composition of this drug product were also selected based on the intent to manufacture a product that can meet all quality/critical quality attributes of the RLD. The main difference in the formulation of this drug product compared to RLD is the use of sodium chloride as the (b) (4) agent instead of mannitol in RLD. The (b) (4) agent is also removed from the composition of this drug product. The proposed commercial formulation of the drug product as a 5mL unit contains 0.25mg of palonosetron provided as 0.28mg of palonosetron hydrochloride as the active ingredient, and 40mg of sodium chloride, 18mg of sodium citrate dihydrate, 7mg of anhydrous citric acid, (b) (4) and water for injection as the excipients. From the ONDP perspective, the proposed formulation differences are not expected to have any significant impacts on the QTTP and/or quality attributes of the final drug product.

The bulk of applicant's product development studies were concentrated on the selection and determination of the compatibility of the primary container closures with drug product. Compatibility of the proposed container closures were established through appropriate migration and leachable/extractable studies. Additionally, the ability of the selected container closure systems to adequately protect the drug product from the external environment and maintaining sterility was initially examined during the early developmental stability investigations and then further established by formal accelerated and long-term drug product stability studies.

The drug product specification includes testing and acceptance criteria for description (appearance, clarity, and color), identity, assay, related substances, particulates, pH, volume, sterility, endotoxin, and package integrity. Based on Biopharm, Microbiology, and ONDP reviewers' assessments, the proposed specification for Palonosetron Hydrochloride Injection is deemed adequate to assure identity, strength, purity, and quality of the drug product at release and throughout the proposed product shelf-life.

The applicant has submitted sufficient accelerated and long-term stability data from the drug product packaged in both glass vial and pre-filled syringe configurations that support of the proposed drug product expiration dating period of 24 months. Therefore, the expiration period of 24 months for both packaging configurations of the drug product is granted.

In summary, the applicant has provided sufficient CMC information to illustrate the capability of routinely manufacturing Palonosetron Hydrochloride Injection with consistent quality batch to batch and with the same quality attributes as the RLD. Therefore, from the drug product perspective, this application is recommended for **approval.**

C. Manufacturing Process

(b) (4)

The description of manufacturing process provided is consistent with and adequately reflects the manufacturing process development and is considered satisfactory.

In summary, the applicant has provided sufficient information to show that the manufacturing process is robust and capable of producing the drug product, Palonosetron Hydrochloride Injection with consistent quality that meets the proposed drug product specification from batch to batch. Therefore, from the manufacturing process perspective, this application is recommended for **approval**.

Biopharmaceutics

The proposed drug product Palonosetron Hydrochloride Injection contains the same active ingredient and citrate (b) (4) system as the reference listed drug (RLD), Aloxi. However, in the formulation of this drug product the (b) (4) agent, mannitol has been substituted by smaller amount of sodium chloride and the (b) (4) agent, sodium edetate has been omitted. The proposed changes in the drug product formulation are not expected to have any significant impacts on the pharmacologic characteristics of the drug product compared to the RLD.

Based on the following reason, the applicant has argued that in-vivo bioavailability/ bioequivalence bridging study is not required:

1. Both RLD and this drug product are sterile solutions for intravenous administration.
2. The drug product contains the same active ingredient and is to be used for the same indication as the RLD.
3. The only differences between the RLD and the proposed drug product are the substitution of sodium chloride for mannitol as the (b) (4) agent and removal and replacement of sodium edetate with mall amount of citric acid in citrate (b) (4) environment. These changes do not have any significant impacts on pharmacologic characteristics of the drug product or stability of the drug product. Furthermore, data from three batches of the drug product packaged in glass vial or as pre-filled syringes show pH range and osmolity closely comparable to RLD at release and throughout proposed shelf-life.

Although due to the formulation differences noted this drug product does not entirely satisfy the biowaiver criteria according 21 CFR 320.22.(b)(1), it is concluded that the information provided is adequate to bridge BA/BE between the RLD and the proposed drug product according to 21 CFR 320.24(b)(6).

In conclusion, from the Biopharmaceutics perspective, this application is recommended for **approval**.

D. CDRH Consult

The review of the drug product packaged as 5-mL unit in a pre-filled syringe required CDRH consult as the drug product in pre-filled syringe is considered a drug-device combination product.

The proposed syringe performance and biocompatibility for the syringe components provided in DMF (b) (4) has been reviewed by the CDRH reviewer, Dr. Sapana Patel. Dr. Patel has concluded that DMF (b) (4) is deficient. An IR has been submitted to the DMF holder on 02/03/2016 requesting that DMF holder should perform some additional testing to address the DMF deficiencies. Although the DMF holder has agreed to perform the additional testing to address the DMF

deficiencies, to-date the deficiencies noted in the IR letter remains outstanding. Therefore, from the CDRH perspective, Dr. Patel has recommended **disapproval** of the syringe as the device in this drug-device combination product until the DMF (b) (4) deficiencies are appropriately addressed (see CONSULT REV-NONCDER-05(Consult Review from CDRH) in DARRTS).

However, from the OPQ perspective the absence of the resolution to the DMF (b) (4) deficiencies identified by Dr. Patel have little no impact on drug product identity, strength, purity, quality, and stability per Microbiology Review. Therefore, the final decision on the action for this application is deferred to OND.

E. Microbiology

The final drug product solution (b) (4) The applicant's proposed environment monitoring and control program for the manufacture of the sterile drug product is also considered adequate.

The information provided in the referenced DMFs regarding the (b) (4) of the primary container closures have been reviewed and found to be adequate.

The proposed sterility and endotoxin testing methods and acceptance criteria in the drug product specification are considered adequate and the sterility and endotoxin testing methods are based on the USP methods and have been adequately validated for testing of this drug product.

The results package integrity testing also indicates that the proposed packaging configurations are capable of protecting the drug product from the external environment and maintain the product sterility.

In conclusion, from the microbiology perspective, no deficiency is noted and this application is recommended for **approval.**

F. Facilities

The overall recommendation for the facilities involved in this application from the Office of Process and Facilities is still **pending.**

G. Environmental Assessment

The applicant's request for the categorical exclusion from the preparation of the environmental assessment according to 21 CFR § 25.31(a) is valid and therefore, granted.

H. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Palonosetron Hydrochloride Injection
Non Proprietary Name of the Drug Product	Palonosetron Hydrochloride Injection
Non Proprietary Name of the Drug Substance	Palonosetron Hydrochloride
Proposed Indication(s) including Intended Patient Population	1) Prevention of acute and delayed nausea and vomiting associated with the initial and repeated courses of moderately and highly emetogenic cancer chemotherapy. 2) Prevention of postoperative nausea and vomiting for up to 24 hours following surgery
Duration of Treatment	Injected as needed (see the indications above)
Maximum Daily Dose	0.25mg/5mL palonosetron as free base
Alternative Methods of Administration	N/A

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Based on the OPQ review team assessment, the applicant of this NDA has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug substance and drug product. All label/labeling issues have adequately resolved. However, the Office of Process and Facilities has not made the overall recommendation of "Acceptable" for the facilities involved in this application. Therefore, from the OPQ perspective, this NDA is not ready for approval in its present form, per 21 CFR 314.125(b) (13).

Hamid Shafiei, Ph.D.
Application Technical Lead
ONDP, Branch V, Division II

Hamid Shafiei -S

Digitally signed by Hamid Shafiei -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hamid Shafiei -S, 0.9.2342.19200300.100.1.1=2000350820
Date: 2016.04.19 18:13:20 -04'00'

54 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature: Pending

Vipul Dholakia Ph.D.,
OPQ/OPF/DIA/Branch 3
4/1/2016

Vipul Dholakia -S
Digitally signed by Vipul Dholakia -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vipul Dholakia -S, 0.9.2342.19200300.100.1.1=2000342958
Date: 2016.04.19 11:05:56 -04'00'

Secondary Review Comments and Concurrence:

I concur with the "pending" status.
Juandria Williams, PhD; DIA/B3
April 2, 2016

Vidya Pai, signing for Juandria Williams, 19April2016.

Vidya B. Pai -S
Digitally signed by Vidya B. Pai -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vidya B. Pai -S, 0.9.2342.19200300.100.1.1=2001508768
Date: 2016.04.19 11:48:06 -04'00'

ASSESSMENT OF THE BIOPHARMACUETICS

38. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product? Is there any waiver issue?

The Applicant submitted NDA 208109 through 505(b)(2) for palonosetron injection, which is filled into either a single-dose glass vial or prefilled syringe with a strength 0.25 mg/ 5 mL. The listed drug is Aloxi® (palonosetron HCl Injection, 0,075 mg/1.5 mL, and 0.25 mg/ 5 mL), approved under NDA 021372 on July 25, 2003. No in-vitro dissolution is applicable here.

The side-by-side comparison in formulation between the proposed drug product and the listed drug is shown in Table 1.

Table 1. Comparison of the Aloxi and the Applicant's palonosetron injection formulations (Highlighted shows the difference between the two formulations)

Ingredient	Function	Aloxi Formulation (mg/mL) (Listed Drug)	Fresenius Formulation (mg/mL) (Proposed drug product)
Palonosetron hydrochloride	**Active ingredient**	0.056 mg/mL or 0.05 mg/mL as base	0.056 mg/mL or 0.05 mg/mL as base
Mannitol USP	(b) (4)	41.5 mg/mL	Not used
Sodium chloride, USP		Not used	8.0 mg/mL
Edetate disodium dihydrage, USP		(b) (4)*	Not used
Sodium citrate dehydrate, USP		3.7 mg/mL	3.6 mg/mL
Citric Acid, Anhydrous, EP		Not used	1.4 mg/mL
Citric Acid Monohydrate, USP		(b) (4)*	Not Used
(b) (4)		(b) (4)	
Water for injection			(b) (4)

**These information was found from internal NDA review source (not provided by the sponsor). During FOI process, the information should be redacted, if necessary.*

The Applicant submitted a request for waiver for in vivo studies for palonosetron injection, 0.25 mg/ 5 mL, in accordance with 21 CFR 320.22(b)1, which states that for certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. The justifications from the Applicant are:

1.The proposed drug product is a sterile liquid intended solely for administration by intravenous injection.
2. The proposed drug product has the same active ingredient in the same concentration 0.05 mg/mL as the reference drug.
3. The proposed drug label seeks the same indications as those listed in the approved label for listed drug (LD) Aloxi, [redacted] (b) (4).
4. The proposed product is identical to the LD except for the substitution of sodium chloride for mannitol as a [redacted] (b) (4) agent and the removal of edetate disodium dihydrate as a [redacted] (b) (4) agent. The substitution of [redacted] (b) (4) agents will not affect the proposed drug product's [redacted] (b) (4) characteristics, and with the help of [redacted] (b) (4) stopper, the removal of [redacted] (b) (4) agent will not affect the stability of the proposed drug product.

The Applicant conducted the comparison of the proposed drug product and listed drug in pH and osmolality. As Table 2 shows, based on the pH and osmolality data from three lots of the proposed drug product as either vial or pre-filled syringe, the pH and osmolality of the proposed drug are comparable to those of the listed drug.

Table 2. Comparison of FK USA's and Innovator's pH and Osmolality Test Data

Company	Fresenius Kabi USA						RLD (Expiry 12/2017)	
	Vial			Prefilled Syringe				
Lot	Lot 16GI04	Lot 16GI05	Lot 16GI16	Lot 16GK0006	Lot 16GK0007	Lot 16GK0008	Lot 33000510	Lot 33000511
pH	4.8	4.8	4.8	4.8	4.8	4.8	5.0	5.0
Osmolality (Osm/kg)	302	301	299	299	299	300	293	289

Reviewer's Assessment:

Compared to the listed drug Aloxi, the proposed drug product removed the mannitol ([redacted] (b) (4) agent) and edetate disodium dehydrate ([redacted] (b) (4) agent) used in the listed drug formulation, and instead, it used sodium chloride and citric acid as the [redacted] (b) (4) agent and [redacted] (b) (4), respectively.

The proposed drug product submitted under a 505(b)(2) NDA does not fully satisfy the criteria for a waiver of evidence of in vivo bioavailability under 21 CFR 320.22(b)(1). Under this regulation, a drug product's in vivo bioavailability or bioequivalence may be considered self-evident and a waiver of in vivo studies may be granted if the drug product meets the following criteria:

• It 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.

Therefore, due to the difference in inactive ingredients between the proposed drug product and the listed drug product, the proposed drug product does not meet the above requirements for a waiver of in vivo bioavailability based on self-evidence as specified in 21 CFR 320.22(b)(1).

Although the criteria for a biowaiver under 21 CFR 320.22(b)(1) is not fully met, based on 21 CFR 320.24(b)(6), the FDA can rely on any other approach deemed adequate by FDA to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products. The Applicant provided justifications in the submission to evaluate the impact of the difference in formulation compared to the listed drug on PK.

1. The impact of formulation changes on PK of palonosetron

As Table 1 shows, compared to the approved Aloxi formulation, the current proposed Palonosetron injection formulation removed the mannitol and edetate disodium dehydrate, and instead, it used sodium chloride and citric acid as the (b) (4) agent and (b) (4), respectively. The amount of the newly added inactive ingredients is within the FDA's IID limits as shown below in Table 3.

Table 3. Comparison of inactive ingredient amounts between Fresenius' formulation and the FDA's IID limits

Inactive Ingredient	Amount (mg/mL)	Amount (%)	FDA IID Limit (maximum potency)
Citric Acid (Anhydrous), USP	1.4	0.14	Intravenous – 41.36%
Sodium Chloride, USP	8.0	0.8	IV (infusion); Injection – 45%

FDA = Food and Drug Administration; IID = Inactive Ingredients Database; USP = United States Pharmacopeia
Source: http://www.accessdata.fda.gov/scripts/cder/ig/index.cfm

It is reported from the literature that mannitol can affect the renal clearance of some drugs (i.e. digoxin) by increasing renal blood flow or increasing urine flow rate (Koren et al. Clin Invest Med. 1999. Oct 12(5) 279-84). Based on the approved drug label for Aloxi (palonosetron HCl), after a single intravenous dose of 10 mcg/kg [^{14}C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose. In healthy subjects, the total body clearance of palonosetron was 0.160 ± 0.035 L/h/kg and renal clearance was 0.067± 0.018 L/h/kg. Therefore, the renal clearance pathway contributed ~42% of the total clearance of palonosetron. Considered the potential effect of mannitol on

renal blood flow and urine flow rate, removing mannitol from the formulation as proposed by the Applicant might result in unpredicted influence on renal clearance of palonosetron.

During the formulation development, the Applicant found that (b) (4) However, the Applicant didn't provide any evidence or justification that the removal of edetate disodium dehydrate in their formulation would not affect the pharmacokinetic of palonosetron.

Therefore, the Agency asked the Applicant to address following questions stated in the 74-day letter comments dated on Sept 10, 2015:

1. It is reported that mannitol might affect the renal clearance of the drug. Provide literature data and your justification that removal of mannitol would not affect the in vivo pharmacokinetic performance of palonosetron compared to that of the reference product.
2. Provide literature data and your justification that removal of edetate disodium dehydrate in your proposed drug product as compared to that of the reference product would not affect the in vivo pharmacokinetic performance of palonosetron.

In response to above questions from the Agency, the Applicant submitted the justifications based on literatures on 10/20/2015.

Effects of mannitol on Palonosetron pharmacokinetics and metabolism

a. The small amount in the Aloxi formulation is unlikely to induce a diuretic effect.

b. In vitro, palonosetron is mainly metabolized by CYP2D6, followed by CYP3A4 and CYP1A2. There are no reports of the effect of mannitol on the phase I or II enzymes or transporters, except one study reported that up to 10 mM of mannitol had no in vitro effect on CYP2E1(Clejan LA, Cederbaum AI. role of cytochrome P450 in the oxidation of glycerol by reconstituted systems and microsomes. FASEB J. 1992 Jan 6;6(2):765-70). As described in section (a), there is 1,245 mg of mannitol in 30 mL of palonosetron injection, which equals to ~ 1.38 mM mannitol, and much less than 10 mM. Therefore, the mannitol in palonosetron HCl injection formulation will not affect the metabolism of palonosetron.

c. Although more than 40% of palonosetron is renal eliminated, the system exposure of palonosetron was increased 28% in severe renal impairment patient, dose adjustment is not necessary in patients with any degree of renal impairment (Helsinn healthcare sa. aloxi® (palonosetron hcl) injection. 2014. lugano, Switzerland, helsinn healthcare sa.). Similarly, no dose adjustment is needed for the administration of palonosetron in hepatic impairment patients.

Overall, it is less likely that the existence of mannitol in the listed drug formulation (Aloxi) will affect the renal clearance of palonosetron. Similarly, removing mannitol in the current proposed drug product is unlikely to affect the pharmacokinetic of palonosetron. Furthermore, sodium chloride is present in the human body; therefore, replacement of mannitol with a small amount of sodium chloride present in the proposed drug product into the human body will not affect the pharmacologic characteristics of palonosetron.

Effects of EDTA on Palonosetron pharmacokinetics and metabolism

a. Edetate disodium (EDTA) is included in the reference drug formulation to (b) (4) (b) (4) The small amount of EDTA in the formulation of the listed drug is unlikely to induce any therapeutic chelation effect.

b. Compared to palonosetron, the half-life of EDTA is very short (20-60 min for EDTA vs 40 hrs for palonosetron), 5-6 hrs after dosing, EDTA will be eliminated totally in the systemic circulation, thus, it is unlikely to have meaningful effects on the PK of palonosetron.

c. There is no reported evidence showing that EDTA could directly affect the activity of CYP enzymes. Therefore, it is less likely that EDTA can affect the metabolism of palonosetron.

Therefore, the existence of EDTA in the listed drug formulation is for (b) (4) and will not affect the palonosetron PK. Consequently, removal of EDTA in the current proposed drug product will not affect the palonosetron PK, as far as the Applicant ensure the (b) (4) of the proposed drug product, which is achieved by the (b) (4) stopper.

2. Establish bridging between the proposed drug product and the listed drug

The proposed drug product does not fully satisfy the criteria for a waiver of evidence of in vivo bioavailability under 21 CFR 320.22(b)(1), due to the difference in inactive ingredients compared to the listed drug. Although the proposed drug product does not fully satisfy the criteria for a waiver of evidence of in vivo bioavailability under 21 CFR 320.22(b)(1), the FDA can rely on any other approach deemed adequate by FDA to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products, based on 21 CFR 320.24(b)(6),

The above justifications from the Applicant on the impact of formulation difference compared to the listed drug on PK are acceptable. The removal of mannitol from the

formulation, and replaced with a small amount of sodium chloride present in the proposed drug product into the human body will not affect the pharmacologic characteristics of palonosetron. Similarly, replacement of EDTA in the listed drug with a small amount of citric acid present in the proposed drug product into the human body will not affect the pharmacologic characteristics of palonosetron.

Another minor difference between the proposed drug product and the listed drug is that citric acid anhydrous is used in the proposed drug product, while citric acid monohydrate is used in the listed drug. The only difference between the two compounds is the hydrate group, and the limit of citric acid anhydrous is within FDA's IID limits shown in Table 3.

As Table 2 shows, the pH and osmolality of the proposed drug product are similar compared to those of the listed drug. The specification on pH for the proposed drug product is pH 4.5 to 5.5, which is the same the as the pH specification of the listed drug stated in the label, as well as the pH specification stated in the label of the tentatively approved NDA 203050.

Based on the overall supportive information, it is expected that the bioavailability of the proposed and listed drug products will be similar.

The impact of application of syringe as a device for the delivery of the proposed drug product would be consulted to CDRH.

In conclusion, consistent with 21 CFR 320.24(b)(6), the FDA deemed that the provided information are adequate in establishing the bridge between the proposed product and the listed product in terms of safety and efficacy.

39. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Applicant's Response:

Reviewer's Assessment:

No issue is identified.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

The proposed drug product has the same active ingredient, concentration, route of administration, and similar pH and osmolality as the reference drug. The justifications from the Applicant on the excipient changes of EDTA and mannitol are acceptable. Based on 21 CFR 320.24(b)(6), the submitted information are deemed adequate to establish the bridge (bioavailability/bioequivalence) between the listed and the proposed drug product.

From the Biopharmaceutics perspective, NDA 208109 is recommended for approval.

Peng (Vincent) Duan, Ph.D.
Biopharmaceutics Reviewer
04/13/2016

Peng Duan -S
Digitally signed by Peng Duan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Peng Duan -S, 0.9.2342.19200300.100.1.1=2001127615
Date: 2016.04.19 13:06:34 -04'00'

Secondary Review Comments and Concurrence:

Tapash Ghosh, Ph.D.
Branch Chief (acting)
4/13/2016

Tapash K. Ghosh -S
Digitally signed by Tapash K. Ghosh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300148262, cn=Tapash K. Ghosh -S
Date: 2016.04.19 15:48:57 -04'00'

ASSESSMENT OF MICROBIOLOGY

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity -** (3.2.P.2.)

  The container/closure system used for validation was: Same as the drug product (as shown in exhibit batch records)

  Study/Report # and date: ccit-data-16gk0006.pdf, dated 12/8/2014; ccit-data-16gk0007.pdf, dated 12/8/2014; ccit-data-16gk0008.pdf, dated

12/8/2014; ccit-data-16gi04.pdf, dated 12/8/2014; ccit-data-16gi05.pdf, dated 12/8/2014; ccit-data-16gi16.pdf, dated 12/8/2014;

Test method: dye ingress

Brief description: Twenty syringes with tip caps or 36 vials were immersed in a 1 g/L solution of methylene blue. The external pressure was reduced by 27 kPa for 10 minutes. Atmospheric pressure was then restored, and the testing samples remained immersed for an additional 30 minute. For the 2 positive controls hypodermic needles with an external diameter of 0.8 mm were used for piercing. Subsequently, the samples were visually analyzed for dye intrusion. The negative controls and the test samples did not demonstrate dye intrusion when analyzed visually; the positive controls demonstrated presence of the dye. Photographs for the visual studies were included. Samples were also scanned for UV absorption at 250-700nm. It is stated that all units for container closure integrity testing are processed using routine production parameters for preparation. Worst case parameters are used for sterilization. The same tests were performed on three lots of syringe configuration: 16GK0006, 16GK0007, and 16GK0008, and three lots of vial configuration: 16GI04, 16GI05, 16 GI16.

Sensitivity: The test is sensitive enough to detect an intrusion of <1 µl of dye in the 5 ml fill volume proposed for the DP.

Note to Reviewer: The applicant states that "The sensitivity of the ingress test is ≥ 0.5 µg methylene blue [1 g/L] in 3 mL solution". 0.5 µg is equal to the amount of 0.5 µL methylene blue [1 g/L]. Therefore it is interpreted that this method is able to detect 0.8 µL of methylene blue [1 g/L] intruded to a 5 mL filled vial.

Results for syringe configuration:

Sample	# Positive/ # Tested
Test Units	0/20x3
Positive Control	2x3/2x3
Negative Control	0/2x3

Results for vial configuration:

Sample	# Positive/ # Tested
Test Units	0/36x3
Positive Control	2x3/2x3
Negative Control	0/2x3

Reviewer's Assessment: Acceptable

23 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CDER/OPQ/OPF/DMA Branch II

Yuansha Chen -S

Digitally signed by Yuansha Chen -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuansha Chen -S, 0.9.2342.19200300.100.1.1=2000813288
Date: 2016.04.19 14:40:42 -04'00'

Secondary Review Comments and Concurrence:

I concur

Nandini Bhattacharya, Ph.D.
QAL (Acting)
CDER/OPQ/OPF/DMA Branch II
4.7.2016

Nandini Bhattacharya -S

Digitally signed by Nandini Bhattacharya -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000589817, cn=Nandini Bhattacharya -S
Date: 2016.04.19 18:03:26 -04'00'

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

44. Is the applicant's claim for categorical exclusion acceptable?

The applicant has claimed categorical exclusion from the environmental assessment analysis according to 21 CFR § 25.31(a), since the action of this application does not increase the use of the active moiety, palonosetron hydrochloride. According to 21 CFR § 25.15(d), the applicant has also stated that to the best of their knowledge, no extraordinary circumstances exist that would significantly affect the quality of the human environment and would warrant the preparation of an Environmental Assessment for Palonosetron Hydrochloride, under 21 CFR § 25.21

Reviewer's Assessment:

Since this is a 505(b)(2) application for a drug product containing a previousely approved active moiety and the drug product is to be used for the same indication at the same dosage strength, oit is not expected to increase the use of the active moiety. Therefore, the applicant's request for categorical exclusion is considered valid. And since to the best of applicant's knowledge no extraordinary circumstances exist that can significantly affect the quality of the human environment, the gategorical exclusion from the environmental assessment analysis is granted.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
The categorical from the preparation of the environmental assessment is granted.

Hamid Shafiei, Ph.D.
Branch V/DNDP II
ONDP/OPQ

Hamid Shafiei -S
Digitally signed by Hamid Shafiei -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hamid Shafiei -S, 0.9.2342.19200300.100.1.1=2000350820
Date: 2016.04.19 12:57:45 -04'00'

Secondary Review Comments and Concurrence:
I agree with Dr. Shafiei's assessment.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP/OPQ

Moojhong Rhee -S
Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2016.04.19 13:20:48 -04'00'

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For ANDA only

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☐ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☐ Yes ☐ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

Reviewer's Assessment:

b) HOW SUPPLIED section

i) Is the information accurate? ☐ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☐ Yes ☐ No
If "No," explain.

Reviewer's Assessment:

c) DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☐ N/A
If "No," explain.

Reviewer's Assessment:

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No
If "No," explain.

Reviewer's Assessment:

e) For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

Reviewer's Assessment:

For NDA only

1. Package Insert

The following is a summary of the labeling review.

The Label/labeling of this drug product is performed to be as much consistent as the previously approved drug product, Aloxi. Especially, the established name for the drug substance is kept as *palonosetron hydrochloride* even though it deviates from the current CDER salt policy by taking the historical exception prescribed in the policy.

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PALONOSETRON HYDROCHLORIDE INJECTION safely and effectively. See full prescribing information for PALONOSETRON HYDROCHLORIDE INJECTION.

PALONOSETRON HYDROCHLORIDE injection, for intravenous use
Initial U.S. Approval: 2003

----------**DOSAGE FORMS AND STRENGTHS**----------
Injection: 0.25 mg palonosetron in 5 mL (0.05 mg/mL) in a single-dose vial or a pre-filled syringe (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Palonosetron Hydrochloride Injection	Proprietary name chosen for this product is the same as the established name. **Satisfactory**
Dosage form, route of administration	Injection 0.25mg/5mL	Dosage form and route of administration are provided. **Satisfactory**
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Injection; 0.25 mg palonosetron in 5 mL (0.05 mg/mL) in a single-dose vial or a pre-filled syringe	The dosage forms and strengths are described correctly. **Satisfactory**

Conclusion:
The Highlights Section of the PI is Adequate.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Palonosetron Hydrochloride Injection is sterile, clear, and colorless:

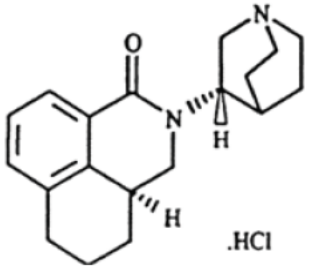
- 0.25 mg palonosetron in 5 mL (0.05 mg/mL) in a single-dose vial or pre-filled syringe

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Injection	Provided **Satisfactory**
Strengths: in metric system	0.25 mg palonosetron in 5 mL (0.05 mg/mL) in a single-dose vial or pre-filled syringe)	Provided **Satisfactory**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Clear colorless solution in a single-dose vial or pre-filled syringe	Appropriately described **Satisfactory**

Conclusion:
The Dosage Forms and Strengths Section of the PI is Adequate.

#11: Description (21CFR 201.57(c)(12))

Palonosetron Hydrochloride Injection contains palonosetron as palonosetron HCl, an antiemetic and antinauseant agent. It is a serotonin-3 (5-HT3) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron HCl is: (3aS)-2[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Palonosetron HCl exists as a single isomer and has the following structural formula:

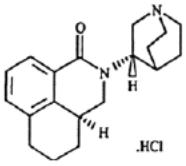


Palonosetron HCl is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

Palonosetron HCl Injection is a sterile, clear, colorless, non pyrogenic, isotonic, buffered solution for intravenous administration. Palonosetron HCl Injection is available as 5 mL single-dose vial or a 5 mL single-dose prefilled syringe.

Each 5 mL vial and prefilled syringe contains: 0.25 mg palonosetron base equivalent to 0.28 mg palonosetron HCl, 40 mg sodium chloride, 18 mg trisodium citrate dihydrate, 7 mg citric acid anhydrous, and water for injection.

The pH of the solution in the 5 mL vial and prefilled syringe is 4.5 to 5.5.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Palonosetron Hydrochloride Injection	Proprietary name chosen for this product is the same as the established name. **Satisfactory**
Dosage form and route of administration	Injection for intravenous use	Provided. **Satisfactory**
Active moiety expression of strength with equivalence statement for salt (if applicable)	0.25 mg palonosetron base equivalent to 0.28 mg palonosetron HCl	Active moiety expression is consistent with approved RLD, Aloxi. **Satisfactory**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Each 5 mL vial and prefilled syringe contains: 0.25 mg palonosetron base as 0.28 mg palonosetron hydrochloride, 40 mg sodium chloride, 18 mg trisodium citrate dihydrate, 7 mg citric acid anhydrous, and water for injection.	This is an injectable drug product and quantitative amounts of the inactive ingredients are appropriately provided. **Satisfactory**
Statement of being sterile (if applicable)	Palonosetron Hydrochloride Injection is a sterile, clear, colorless, non-pyrogenic, isotonic, buffered solution for intravenous administration.	Provided. **Satisfactory**
Pharmacological/ therapeutic class	Palonosetron Hydrochloride Injection contains palonosetron as free base, an antiemetic and antinauseant agent.	Pharmacological/ therapeutic class is provided. **Satisfactory**
Chemical name, structural formula, molecular weight	Chemical Name: (3aS)-2[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline hydrochloride Structural formula:  Molecular weight: 332.87 Empirical formula: $C_{19}H_{24}N_2O \cdot HCl$	All necessary information provided. **Satisfactory**
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as	Palonosetron hydrochloride is a white to off-white crystalline	Provided.

pKa, solubility, or pH)	powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.	**Satisfactory**

Conclusion:
The Description Section of the PI is adequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Palonosetron Hydrochloride Injection is clear and colorless and is supplied in single-dose vials and pre-filled syringe as follows:

NDC Number	Strength	Package
63323-942-41	0.25 mg/5 mL (0.05 mg/mL)	1 vial/carton
63323-942-05	0.25 mg/5 mL (0.05 mg/mL)	10 vials/carton
63323-942-42	0.25 mg/5 mL (0.05 mg/mL)	1 pre-filled syringe/carton
63323-942-90	0.25 mg/5 mL (0.05 mg/mL)	10 pre-filled syringes/carton

Storage

- Store at 20° to 25°C (68° to 77°F) [" (b) (4)].
- Protect from freezing.
- Protect from light.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Palonosetron Hydrochloride Injection, 0.25mg/5mL	Strength provided **Satisfactory**
Available units (e.g., bottles of 100 tablets)	Palonosetron Hydrochloride Injection is clear and colorless and is supplied in single-dose vials and pre-filled syringe as follows: • 0.25 mg/5 mL (0.05 mg/mL) 1 vial/carton • 0.25 mg/5 mL (0.05 mg/mL) 10 vials/carton • 0.25 mg/5 mL (0.05 mg/mL) 1 pre-filled syringe/carton • 0.25 mg/5 mL (0.05 mg/mL) 10 pre-filled syringes/carton	**Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	• NDC No. 63323-942-41 1 vial/carton • NDC No. 63323-942-0510 vials/carton • NDC No. 63323-942-42 1 pre-filled syringe/carton • NDC No. 63323-942-90 10 pre-filled syringe/carton	Provided. **Satisfactory**
Special handling (e.g., protect from light, do not freeze)	• Protect from freezing. • Protect from light.	Provided. **Satisfactory**
Storage conditions	Store at 20° to 25°C (68° to 77°F) [(b) (4)]	Provided. **Satisfactory**

Manufacturer/distributor name listed at the end of PI, following Section #17

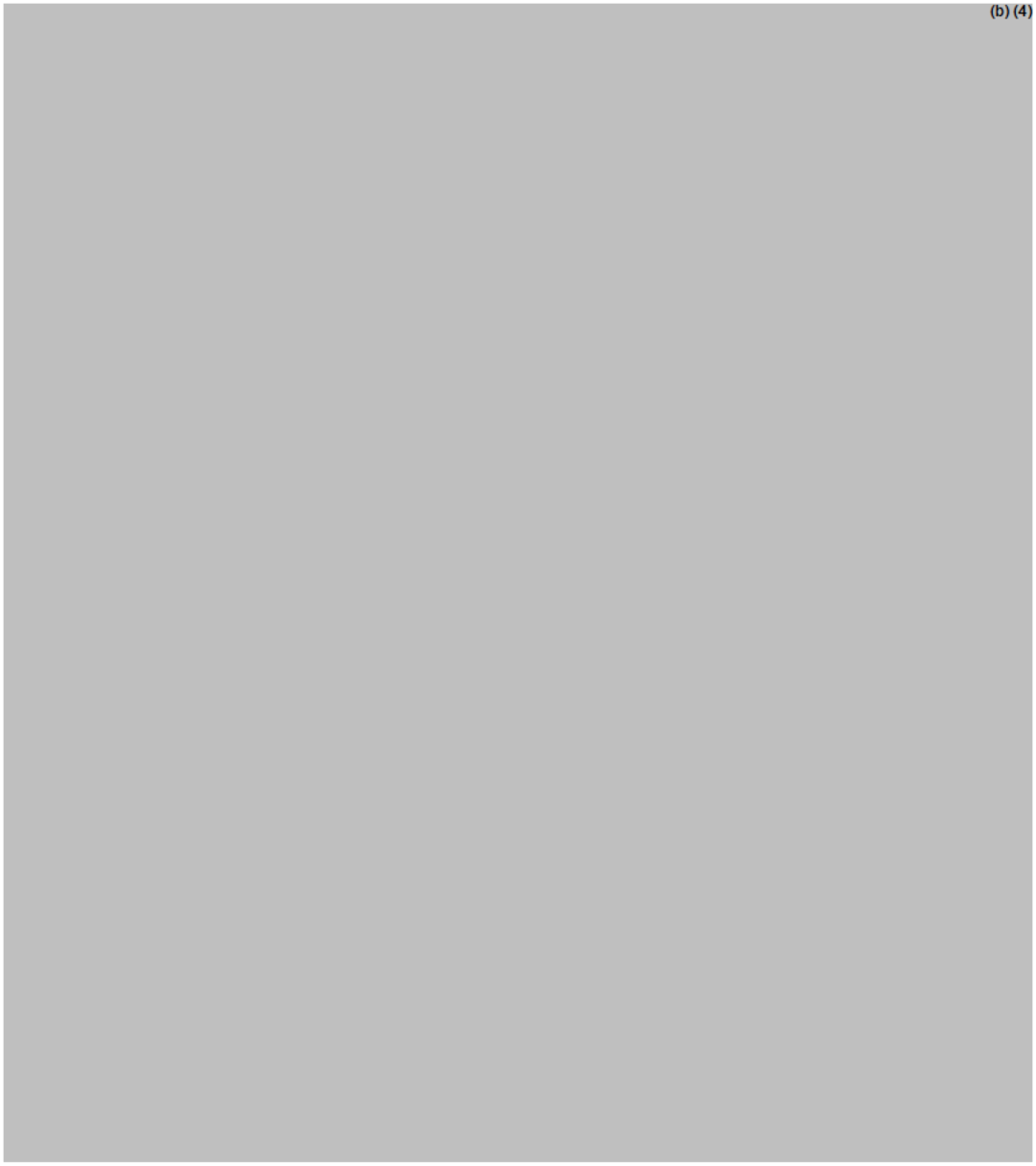
Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: FRESENIUS KABI (b) (4) Lake Zurich, IL 60047 Made in Austria	Provided. **Satisfactory**

Conclusion:
The information provided in sections 16 and 17 of the PI is adequate.

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name and established name for this product is the same. It is presented as Palonosetron Hydrochloride Injection with appropriate font size and prominence that satisfies 21 CFR 201.10(g)(2).	**Satisfactory**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	0.25mg/5mL (0.05mg/mL)	Provided **Satisfactory**
Net contents (21 CFR 201.51(a))	5mL	Provided **Satisfactory**
Lot number per 21 CFR 201.18	The location on the immediate container label where the lot number will be displayed is provided. Satisfies 21 CFR 201.18.	Provided **Satisfactory**
Expiration date per 21 CFR 201.17	The location on the immediate container label where the expiration date will be displayed is provided. Satisfies 21 CFR 201.17.	Provided **Satisfactory**
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" is displayed. Satisfies 21 CFR 201.100(b)(1).	Displayed **Satisfactory**
Storage (not required)	Storage condition displayed.	Provided **Satisfactory**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Displayed	Provided **Satisfactory**
Bar Code per 21 CFR 201.25(c)(2)**	Bar Code is displayed.	Provided **Satisfactory**
Name of manufacturer/distributor	Name of manufacturer/distributor is appropriately displayed.	Displayed **Satisfactory**
Others	Discard unused portion.	Provided **Satisfactory**

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'',

‘‘physician’s sample’’, or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label
**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Inadequate
The immediate container labels are adequate.

2) Carton Labeling

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name and established name for this product is the same. It is presented as Palonosetron Hydrochloride Injection with appropriate font size and prominence that satisfies 21 CFR 201.10(g)(2).	**Satisfactory**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	0.25mg/5mL (0.05mg/mL)	**Satisfactory**
Net contents (21 CFR 201.51(a))	5mL	**Satisfactory**
Lot number per 21 CFR 201.18	The location on the carton where the lot number will be displayed is provided. Satisfies 21 CFR 201.18.	**Satisfactory**
Expiration date per 21 CFR 201.17	The location on the carton where the expiration date will be displayed is provided. Satisfies 21 CFR 201.17.	**Satisfactory**
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Each 5 mL vial and prefilled syringe contains: 0.25 mg palonosetron base as 0.28 mg palonosetron hydrochloride, 40 mg sodium chloride, 18 mg trisodium citrate dihydrate, 7 mg citric acid anhydrous, and water for injection.	This is an injectable drug product and quantitative amounts of the inactive ingredients are appropriately provided. **Satisfactory**
Sterility Information (if applicable)	"Sterile" is displayed.	**Satisfactory**
"Rx only" statement per 21 CFR 201.100(b)(1)	Appropriately displayed. Satisfies 21 CFR 201.100(b)(1).	**Satisfactory**
Storage Conditions	Storage condition displayed.	**Satisfactory**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling) also see 21 CFR	Appropriately displayed. Satisfies 21 CFR 201.2.	**Satisfactory**
Bar Code per 21 CFR 201.25(c)(2)**	The location on the carton where the barcode will be displayed is provided. Satisfies 21 CFR 201.25(c)(2).	**Satisfactory**
Name of manufacturer/distributor	Manufactured for: FRESENIUS KABI (b) (4) Lake Zurich, IL 60047 Made in Austria	

		Satisfactory
"See package insert for dosage information" (21 CFR 201.55)	Usual Dosage: See package insert. Satisfies 21 CFR 201.55.	Provided **Satisfactory**
"Keep out of reach of children" (optional for Rx, required for OTC)	Prescription drug product. This statement is optional and not required.	Not provided. **Satisfactory**
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	For intravenous injection only	provided **Satisfactory**

Conclusion: Inadequate
The carton labels are adequate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The package insert, immediate containers, and cartons label/labeling adequately satisfy all current drug product label/labeling requirements and therefore, are deemed **satisfactory** from the ONDP perspective.

Hamid Shafiei, Ph.D.
Branch V/DNDP II
ONDP/OPQ

Hamid Shafiei -S
Digitally signed by Hamid Shafiei -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hamid Shafiei -S, 0.9.2342.19200300.100.1.1=2000350820
Date: 2016.04.19 12:56:36 -04'00'

Secondary Review Comments and Concurrence:
I agree with Dr. Shafiei's assessment.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP/OPQ

Moojhong Rhee -S
Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2016.04.19 12:17:38 -04'00'

II. List of Deficiencies To Be Communicated

Drug Substance

Drug Product

Facility

Biopharmaceutics

Microbiology

Environmental

Label/Labeling

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
Assay and Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Testing for assay and related substance at release and during stability using validated analytical methods	L	None
Physical stability (glass lamination, precipitation, syringe)	• Formulation • Container closure • Raw materials • Process parameters • Site	H	Routinely examined during drug product stability testing program. pH of the product is controlled (4.5 – 5.5). Components of the drug product are frrely water soluble.	L	None
Impurities/related	• Formulation	M	Routinely	L	None

substances/residual solvents	• Container closure • Raw materials • Process parameters • Scale/equipment • Site		tested drug release and stab ility program using validate analytical methods		
Microbial limits/Sterility (as per Quality Microbiology)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	H	Tested at release and periodically during and at the conclusion of the stability testing program using validated USP-based sterility and endotoxin methods	L	None