

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203050Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: March 1, 2016

From: Danuta Gromek-Woods, Ph.D.
CMC Lead (Acting), Branch V/ONDP

Through: Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch V/ONDP

To: CMC Review #2 of NDA 203 050

Subject: Biopharm Addendum to clarify biowaiver for NDA 203 050

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Rhee -S

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In the first review cycle, the applicant requested biowaiver for NDA 203 050, and it was granted (see Biopharmaceutics Review dated Jan-3-2012). However, in conjunction with a recent citizen petition, biowaiver issue was revisited and Biopharmaceutics review team documented an addendum to the original Biopharmaceutics Review, see the **Attachment 1**.

Attachment 1: Biopharm's Memo on Biowaiver

ADDENDUM TO BIOPHARMACEUTICS REVIEW

From: Tien-Mien Chen, Ph.D.

Through: Kelly Kitchens, Ph.D.

To: NDA 203050 for Palonosetron Hydrochloride Injection

Re: Biowaiver Request

This addendum to the Original Biopharmaceutics Review provides clarification regarding the bioavailability/bioequivalence waiver (biowaiver) request for the proposed drug product, Palonosetron Hydrochloride Injection and the listed drug product, Aloxi® under NDA 21372. The Original Biopharmaceutics Review for NDA 203050 dated June 21, 2012, states that the Applicant, Dr. Reddy's Laboratories requested a biowaiver and the biowaiver was granted.

It is noted that the proposed drug product submitted under a 505(b)(2) NDA does not appear to 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.

The listed and proposed drug products have the same strength (b) (4) and same pH; however, the drug product proposed by Dr. Reddy's Laboratories differs from the listed drug product in that it contains sodium acetate rather than sodium citrate (b) (4) and it does not contain disodium edetate (EDTA). (b) (4)

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. Specifically for NDA 203050, the difference in (b) (4) absence of EDTA in the formulation of the proposed drug product is not expected to impact the bioavailability of palonosetron following intravenous administration. The rationale is as follows: EDTA is used in the listed drug product (b) (4)

(b) (4) Absence of EDTA would not be expected to alter the pharmacologic activity of the product.¹

Sodium acetate and sodium citrate (b) (4) are present in the human body; therefore, injection of a small amount of either sodium acetate or sodium citrate (b) (4) present in the listed drug or the proposed drug product into the human body will not affect the pharmacologic characteristics of palonosetron. Based on the overall supportive information, it is expected that the bioavailability of the proposed and listed drug products will be similar.

In conclusion, in the Original Biopharmaceutics Review dated 6/21/2012, consistent with 21 CFR 320.24(b)(6) the FDA deemed adequate the information supporting the relative bioavailability (or bridge) to the Agency's finding of safety and effectiveness for the listed drug.

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

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Kelly Kitchens, Ph.D.
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics-Branch II
Office of New Drug Products, OPQ

¹ Our conclusion is consistent with a published article (Anesthesiology, 88(5): 1170-1182 1998) which indicates that the pharmacokinetic profile of a drug product is not affected by the addition of EDTA to the formulation of the product.

Memorandum

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

Date: February 23, 2016
From: Danuta Gromek-Woods, Ph.D.
Through: Moo-Jhong Rhee, Ph.D.
Branch Chief, ONDP/Branch V
To: CMC Review #2 of NDA 203 050

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Subject: Final Recommendation for Approval of NDA 203 050

The labeling issues noted in Review # 2 have been resolved as per Memorandum dated 22-Feb-2016 prepared by Dr. Zhengfang Ge (see the Attachment I, and Attachment II for the finalized labeling and labels).

Recommendation:

Therefore, this NDA is recommended for approval from the ONDP perspective.

Attachment I:

Memorandum

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

Date: Feb 22, 2016

From: Zhengfang Ge, Ph.D.
ONDP/Division II/Branch V

Zhengfang
Ge -S

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

Moojhong
Rhee -S

To: CMC Review #2 of NDA 203050

Subject: Final labeling/labels

Review Note:

Previous review #2 dated 9-Feb-2016 was concluded with a recommendation for **Not Approval** pending resolution of the labeling issues. It has been decided to use palonosetron hydrochloride as the established name for all the palonosetron products by taking a historical exception from CDER Salt policy. Therefore, the established name proposed in this NDA is adequate.

The applicant provided an updated carton/container labels in response to DMEPA's requests. The final carton container labels (see Appendix) are adequate from CMC perspective.

Conclusion:

The labeling issues noted in review #2 have been resolved. Therefore, the NDA is now recommended for Approval from the drug product perspective.

Attachment II: PI and Container/Carton labels

PI

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 (3)
- 0.075 mg palonosetron in 1.5 mL (0.05 mg/mL) in a single-dose vial (3)

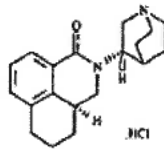
3 DOSAGE FORM AND STRENGTHS

Palonosetron Hydrochloride Injection is sterile, clear, and colorless:

- 0.25 mg palonosetron in 5 mL (0.05 mg/mL) in a single-dose vial
- 0.075 mg palonosetron in 1.5 mL (0.05 mg/mL) in a single-dose vial

11 DESCRIPTION

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: (3a*S*)-2-[(*S*)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride. The empirical formula is C₁₉H₂₄N₂O.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 and 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 1.5 mL single-dose vial.

Each 5 mL vial contains 0.25 mg palonosetron base equivalent to 0.28 mg palonosetron HCl, 207.5 mg mannitol, and 15.0 mg sodium acetate trihydrate and water for intravenous administration.

Each 1.5 mL vial contains 0.075 mg palonosetron base equivalent to 0.084 palonosetron HCl, 62.25 mg mannitol, and 4.5 mg sodium acetate trihydrate, and water for intravenous administration.

The pH of the solution in the 5 mL and 1.5 mL vials is 4.5 to 5.5, hydrochloric acid or sodium hydroxide may have been added to adjust pH.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

<u>NDC Number</u>	<u>Strength</u>	<u>Package</u>
43598-530-07	0.25 mg/5 mL (0.05 mg/mL)	1 vial/carton
43598-531-19	0.075 mg/1.5 mL (0.05 mg/mL)	5 vials/carton

Storage

- Store at 20° to 25°C (68° to 77°F); [Excursions permitted to 15–30 °C (59–86°F)].
 - Protect from freezing.
 - Protect from light.
-

Container Labels

(b) (4)



Carton Labels

(b) (4)







QUALITY ASSESSMENT

**Recommendation:**

This 505(b)(2) application is *not* recommended for **Approval** as of this review, per 314.125(b)(6).

NDA 203050 (Request for Final Approval)

Review # 2

Review Date: February 6, 2016

Drug Name/Dosage Form	Palonosetron Hydrochloride Injection
Strength	0.075 mg/1.5 mL and 0.25 mg/5 mL
Route of Administration	Intravenous Injection
Rx/OTC Dispensed	Rx
Applicant	Dr. Reddy's Laboratories Limited
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
NDA 203050	9/1/2015	Drug Substance, Drug Product
Amendment 0020	1/7/2016	Drug Product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus, Ph.D.	Branch II/New Drug API
Drug Product	Zhengfang Ge, Ph.D.	ONDP/DIVISION II/BRANCH V
Process	N/A	
Microbiology	David Bateman, Ph.D.	OMPT/CDER/OPQ/OPF/DMA/MABII I
Facility	Xiaohui (Sherry) Shen	OMPT/CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Truong Quach, Pharm.D.	OPRO/Branch I
Application Technical Lead	Danuta Gromek-Woods, Ph.D.	OMPT/CDER/OPQ/ONDP/DNDPI
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue	OGROP/ORA/OO/OMPTO/DMPTPO/ MDTP
Environmental Assessment (EA)	N/A	

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
23590	Type II	Dr. Reddy's Laboratories Limited	Palonosetron Hydrochloride	Adequate	2-Dec-2015	Reviewed by J. Leginus

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
CMC Review #1	203050	8/10/2012 CMC Review of Original Application
CMC Memo	203050	10/22/2012 ONDQA Final Recommendation of Approval

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has issued an overall "Acceptable" recommendation for the facilities involved in this application, on 05-Feb-2016.

However, issues on the label/labeling are still pending as of the date of this review.

Therefore, from the ONDP perspective, this NDA is not recommended for approval at this time in its present form per 21 CFR 314.125(b)(6), pending resolution of the labeling issues.

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

N/A

II. Summary of Quality Assessments

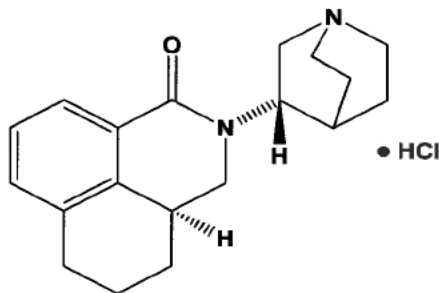
The Original NDA 203050 for Palonosetron Hydrochloride 0.075 mg/1.5 mL and 0.25 mg/5 mL was submitted on 03-Jan-2012. CMC Review #1 was placed in DARRTS on 22-Oct-2012 with a final recommendation for approval. NDA 203050 was Tentatively Approved on 2-Nov-2012 due to an ongoing patent infringement suit.

A. Drug Substance, Palonosetron Hydrochloride, Quality Summary

1. Chemical Name or IUPAC Name/Structure

CAS Number: [135729-62-3]

Structural Formula:



Molecular Formula: $C_{19}H_{24}N_2O \cdot HCl$
Molecular Weight: 332.87

From the drug substance perspective, this resubmission provides for addition of alternate manufacturing site ((b) (4)) for drug substance supplied by the same manufacturer (Dr. Reddy's Laboratories Limited) under the same DMF (# 23590). Dr. Reddy's has filed a DMF originally from their (b) (4) on 01-Mar-2010 and subsequently the DMF has been amended on 28-Aug-2015 to incorporate (b) (4) an alternate manufacturing facility, Dr. Reddy's (b) (4).

The Applicant references the Type II DMF 23590 for details on the description, characterization, manufacture, packaging, specification for quality control testing, and stability of the proposed drug substance, palonosetron hydrochloride.

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

In conclusion, as per drug substance reviewer, Dr. J. Leginus, the data is adequate to support the use of palonosetron hydrochloride drug substance in the manufacture of palonosetron drug product.

B. Drug Product Palonosetron Hydrochloride Quality Summary

This resubmission was submitted on 01-Sep-2015 as a Request for Final Approval claiming resolution of the patent issues, with the following new CMC information with regard to the drug product:

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

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

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

Based on the Facility Assessment, there appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the involved facility’s inspection results, inspectional history, and relevant experience.

The Office Process and Facility made a recommendation of approval for Palonosetron Hydrochloride Injection 0.075 mg/1.5 mL and 0.25 mg/5 mL.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	None
Non Proprietary Name of the Drug Product	Palonosetron Hydrochloride Injection
Non Proprietary Name of the Drug Substance	NA
Proposed Indication(s) including Intended Patient Population	<ul style="list-style-type: none"> • Moderately emetogenic cancer chemotherapy prevention of acute and delayed nausea and vomiting associated with initial and repeat courses • Highly emetogenic cancer chemotherapy prevention of acute nausea and vomiting associated with initial and repeat courses • Prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated

D. Biopharmaceutics Considerations

1. BCS Classification:
 - Drug Substance: BCS 1
 - Drug Product: NA
2. Biowaivers/Biostudies
 - Biowaiver Requests: N/A
 - PK studies: N/A
 - IVIVC: N/A

E. Novel Approaches

F. Any Special Product Quality Labeling Recommendations:

- Per Labeling and Nomenclature Committee’s recommendation, the established name is decided to be “**palonosetron hydrochloride**” taking a historical exception from the CDER Salt policy.

G. Life Cycle Knowledge Information (see Attachment A)



OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Danuta Gromek-Woods, Ph.D.
CMC Lead
ONDP/Div II/Branch V

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This facility is considered acceptable to perform manufacturing, packaging and quality control and stability testing, for drug product.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

There appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA 203050.

Sherry Xiaohui Shen, CSO
February 5, 2016

Xiaohui S. Shen -S

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Date: 2016.02.08 16:49:45 -05'00'

Secondary Review Comments and Concurrence:

I concur.
Grace E. McNally, Branch Chief (acting), OPQ/OPF/DIA/B3
February 5, 2016

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McNally
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ASSESSMENT OF THE BIOPHARMACEUTICS

(Not applicable)



QUALITY ASSESSMENT



23. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Applicant's Response:

Reviewer's Assessment:

24. 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:

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

N/A

Secondary Review Comments and Concurrence:

N/A

ASSESSMENT OF MICROBIOLOGY

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

Applicant's Response:

P.3.5 Process Validation and/or Evaluation

-  (b) (4)

Acceptable





(b) (4)

Acceptable



(b) (4)

Acceptable

- P.5 Control of Drug Product**
- P.5.1 Specification**

No changes were made to the specifications which are shown in the table below.

Acceptable**P.8 Stability****P.8.1 Stability Summary and Conclusion**

Proposed Expiry: A shelf life extension from (b) (4) to 24 months is proposed.

P.8.3 Stability Data

Acceptable sterility and bacterial endotoxins data from long term stability studies are provided for the original submission batches RH001, RH004, RH005, RJ001, RJ002 and RJ003 to support the proposed 24 months shelf life extension. The bacterial endotoxins results were less than (b) (4) EU/mg and met the NMT (b) (4) EU/mg specification, and all samples complied with the sterility test specification at the initial, 6 month, 12 months and 24 months testing periods.

Acceptable**Reviewer's Assessment: ACCEPTABLE**

The Division of Microbiology has no additional comments at this time.

2.3.P.7 Container/Closure System

26. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment:

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

27. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment:

28. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

The Division of Microbiology recommends **APPROVAL** of NDA 203050, Palonosetron hydrochloride Injection.

12/15/15



QUALITY ASSESSMENT



David Bateman, Ph.D.
Microbiology Reviewer
Division of Microbiology/OPF
Office of Pharmaceutical Quality

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Bateman -S

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Date: 2016.02.08 23:01:18 -05'00'

Secondary Review Comments and Concurrence:

I concur on behalf of Stephen Langille, Microbiology Branch Chief
Dupeh Palmer, Ph.D. / Microbiology Secondary Reviewer
12/15/15

Dupeh R.
Palmer-
ochieng -S

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

- 29. Is the applicant's claim for categorical exclusion acceptable?
- 30. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

NA

Secondary Review Comments and Concurrence:

NA

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

Labeling & Package Insert: Labeling issues are under discussion and pending.

II. List of Deficiencies To Be Communicated

Label/Labeling: The labeling and labels have not been finalized as of this review.

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
		H, M, or L		Acceptable or Not Acceptable	

Memorandum

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 22-Oct-2012
To: CMC Review #1 for NDA 203050
From: Bogdan Kurtyka, Ph.D.
CMC Reviewer, ONDQA Division II
Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV ONDQA Division II
CC: Marie Kowblansky, Ph.D.
CMC Lead, ONDQA Division II
Subject: **Final Recommendation and Expiration Dating
Period Status for NDA 203050**

Previous CMC Review #1 dated 08-Aug-2012 noted following deficiencies with a recommendation of “Non Approval” action.

Label/labeling issues:

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

*Palonosetron Hydrochloride Injection.
0.075 mg/1.5 mL and 0.25 mg/5 mL*

This memorandum is to finalize the CMC Review #1, since the sponsor addressed above issues satisfactorily in the submissions dated 05-Oct-2012 and 16-Oct-2012..

Also, this memorandum is to elaborate on the decision on the previously granted expiration dating period of 12-month even 18-month stability data are available.

Stability data:

- *In the original application the sponsor provided 6 months accelerated and 12 months long term stability data with a proposed 24 months expiration dating period.*
- *In the amendment dated 12-Jul-2012, the sponsor submitted 18 months of long-term stability data. However, in the amendment dated 06-Aug-2012, the sponsor changed the proposed 24 months expiration dating period to (b) (4) months.*

Stability Issues:

- *During the review of the stability data submitted in the original application, one of the stability batch showed a significant change in unidentified impurity (RRT= (b) (4)) at 6 months of accelerated conditions.*
- *The same impurity was also observed significantly at the 12 months under the long-term conditions. On request from the Agency, the sponsor submitted an investigation report, which indicated that the problem was originated from the integrity of coating used on vial stoppers.*

- [Redacted] (b) (4)

- [Redacted] (b) (4)

Recommendation and Conclusion:

Because of satisfactory resolution of labeling issues and adequate expiration dating period, from the ONDQA perspective, this NDA is now recommended for “Approval”.

Review Notes

Deficiency 1.

The amount of sodium chloride has been added to Section 11 of the package insert.

Deficiency 2.

Container and carton labels include the established name listed on one line, as shown below:



The carton for the 0.25 mg/5 mL strength is similar except the strength expression.

It is noted that the word "hydrochloride" on the container labels is abbreviated as "HCl", as shown below for the 0.075 mg/1.5 mL label. The carton for the 0.25 mg/5 mL strength is similar except the strength expression.

According to the sponsor, this was necessary due to the limited space on the vial label. After consultation with the DMEPA reviewer, Dr. Denise Baugh, this change was found acceptable.

Overall Evaluation: The submitted information is ADEQUATE and successfully resolved the issues listed in the Review #1.

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/s/

BOGDAN KURTYKA
10/22/2012

MOO JHONG RHEE
10/22/2012
Chief, Branch IV

NDA 203-050

Palonosetron Hydrochloride Injection 0.075 mg/1.5 mL and 0.25 mg/5 mL

Dr. Reddy's Laboratories Ltd.

Bogdan Kurtyka, Ph.D.
Review Chemist

**Office of New Drug Quality Assessment
Division New Drug Quality Assessment II
Branch IV**

**CMC REVIEW OF NDA 203-050
For the Division of Gastroenterology and Inborn Errors Products
(HFD-180)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 203-050

2. REVIEW #: 1

3. REVIEW DATE: 08-Aug-2012

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	03-Jan-2009
Amendment	12-Jul-2012
Amendment	06-Aug-2012

7. NAME & ADDRESS OF SPONSOR:

Name: Dr. Reddy's Laboratories Limited
Address: Bachepally 502 325
India
US Agent: Dr. Reddy's Laboratories, Inc.,
200 Somerset Corporate Blvd, 7th Floor,
Bridgewater, NJ 08807
Telephone: 908-203-7022
Fax: 908-203-4980

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None
- b) Non-Proprietary Name: Palonosetron hydrochloride injection
- c) Code Name/# (ONDQA only): None
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: S

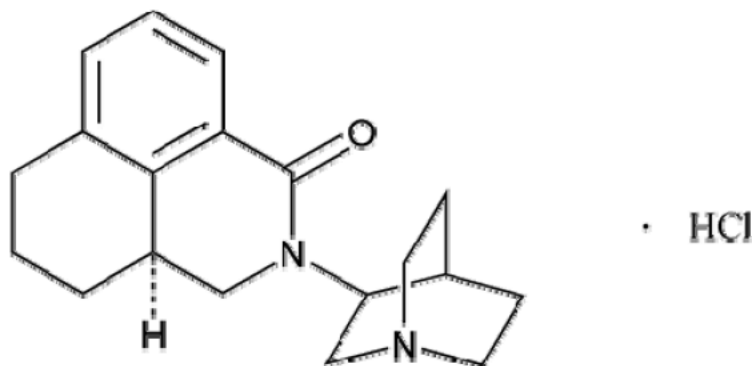
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Serotonin subtype 3 (5-HT₃) receptor antagonist
11. DOSAGE FORM: Injection CODE: 700
12. STRENGTH/POTENCY: 0.075 mg/1.5 mL and 0.25 mg/5 mL
13. ROUTE OF ADMINISTRATION: Intravenous CODE: 002
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (3*aS*)-2,3,3*a*,4,5,6-Hexahydro-2-[(3*S*)-3-quinuclidinyl]-1*H*-benz[*de*]isoquinolin-1-one monohydrochloride
USAN Name: Palonosetron hydrochloride
CAS Number: 135729-62-3
Structural Formula:



Molecular Formula: C₁₉H₂₄N₂O * HCl
Molecular Weight: 332.87

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
23590	II	Dr. Reddy's Labs	Palonosetron hydrochloride	3	Adequate	15-Dec-2010, checked into DARRTS on 15-Mar-2011	Reviewed by Shahnaz Read, Ph.D.
(b) (4)	III		(b) (4)		N/A	N/A	
	III			3	Adequate	10-Oct-2002	Reviewed by Elsbeth Chikhale., Ph.D.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	24-FEB-2012	Bogdan Kurtyka, Ph.D.
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A	18-MAR-2010	Walter Fava
EA	Categorical exclusion granted (see review)	01-JUN-2012	Bogdan Kurtyka, Ph.D.
Microbiology	Acceptable	20-MAR-2012	Steven Donald, Ph.D.

Executive Summary Section

The CMC Review for NDA 203-050

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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

The office of Compliance has issued an overall recommendation of “Acceptable” for the facilities involved in this application (see the **Attachment**, p. 46).

However, issues on the label/labeling are still pending as of the date of this review (see the **List of Deficiencies**, p.45).

Therefore, from the ONDQA perspective, this NDA is *not* recommended for approval per 21CFR 314.125(b)(6) in its present form until the above issues delineated in the “**List of Deficiencies**” (p. 45) are satisfactorily resolved.

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

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The sponsor references DMF 23590 (Dr. Reddy’s Laboratories, Inc.) for details on the description, characterization, manufacture, packaging, specification for quality control testing, and stability of the proposed drug substance, palonosetron hydrochloride. A letter of authorization to cross reference the DMF is provided in the application. ^{(b) (4)}

(2) Drug Product

Palonosetron hydrochloride injection is indicated for prevention of nausea and vomiting following chemotherapy or operations. It is a clear, colorless solution. The inactive ingredients of the formulation are commonly used in injection drug products. All excipients are listed in the Inactive Ingredients Database and the proposed amounts do

Executive Summary Section

not exceed previously approved levels. The drug product is manufactured by (b) (4)

Two strengths, 0.075 mg/1.5 mL and 0.25 mg/5 mL are proposed. The sponsor proposed Gland Pharma Limited (b) (4) India) as the manufacturing site.

The drug product specification includes: appearance, identification, pH, assay, clarity of solution, impurities, (b) (4) extractable volume, particulate contamination, bacterial endotoxins, sterility, and osmolar ratio. The specification attributes and their analytical methods and acceptance criteria are deemed satisfactory for assuring the identity, strength, purity, and quality.

The container closure system consists of 2 mL and 5 mL glass vials with rubber stoppers and sealed flip-off seals. The information included in the application demonstrates that the proposed container/closure system meets all recommendations of relevant USP monographs and the Agency's guidance.

The sponsor provided the results of 18 months long-term stability studies, and the proposed an (b) (4) month expiration dating period under the controlled room conditions is granted.

The applicant claimed categorical exclusion from the Environmental Assessment based on 21CFR 25.31(a).

B. Description of How the Drug Product is Intended to be Used

The drug product should be as a single IV dose, administered over 10 to 30 seconds, 30 minutes before start of chemotherapy or immediately before the induction of anesthesia.

C. Basis for Not-Approval Recommendation

21CFR 314.125(b)(6)

- Prescribing Information does not have the required information on the inactive ingredient.
- For the established name in the labels, "palonosetron" and "hydrochloride" should be presented in the same line as follows:

Palonosetron Hydrochloride Injection.
0.075 mg/1.5 mL (or 0.25 mg/5 mL)

(see the **List of Deficiencies** on p.45).

Executive Summary Section

III. Administrative

- A. Reviewer's Signature:** *(See appended electronic signature page)*
Bogdan Kurtyka, Ph.D.
CMC Reviewer, Branch IV/Division II/ONDQA
- B. Endorsement Block:** *(See appended electronic signature page)*
Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV/Division II/ONDQA
- C. CC Block:** Entered electronically in DARRTS

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CMC Assessment Section

request for explanation of observed trends and additional stability data. The response is discussed in the “Stability Summary and Conclusion” section of this review. **ADEQUATE.**

A APPENDICES

A.1 Facilities and Equipment (biotech only) N/A

A.2 Adventitious Agents Safety Evaluation N/A

A.3 Novel Excipients N/A

R REGIONAL INFORMATION

R1 Executed Batch Records

For executed batch record for drug substance the application refers to DMF 23590.

The application contains executed batch records for selected stability batches. The Executed batch records are consistent with the manufacturing procedures described in this application. **ADEQUATE.**

R2 Comparability Protocols N/A

R3 Methods Validation Package N/A

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

1. Package Insert

(a) “Highlights” Section

Palonosetron Hydrochloride Injection for Intravenous Use
Initial U.S. Approval: 2003

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	Established name is given as palonosetron Satisfactory
Dosage form, route of administration	Injection for intravenous use Satisfactory
Controlled drug substance symbol (if applicable)	N/A

CMC Assessment Section

Dosage Forms and Strengths (201.57(a)(8))	0.25 mg/5ml (b) (4) single (b) (4) vial 0.075 mg/1.5ml (b) (4) single (b) (4) vial Satisfactory
Whether the drug product is scored	N/A

Evaluation: The “**Highlights**” section is adequate.

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths

Palonosetron hydrochloride injection is (b) (4) clear, colorless (b) (4):

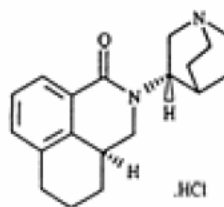
- 0.25 mg (b) (4) per 5 ml
- 0.075 mg (b) (4) per 1.5 ml

Item	Information Provided in NDA
Available dosage forms	Injection Satisfactory
Strengths: in metric system	0.25 mg (b) (4) per 5 ml 0.075 mg (b) (4) per 1.5 ml Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	(b) (4) Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	clear, colorless solution in glass vials Satisfactory

Evaluation: The “**Dosage Forms and Strengths**” section is adequate.

#11: Description

Palonosetron hydrochloride (b) (4) an antiemetic and antinauseant agent. It is a serotonin subtype 3 (5-HT₃) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is: (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-*H*benz[*de*]isoquinoline hydrochloride. The empirical formula is C₁₉H₂₄N₂O.HCl, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:



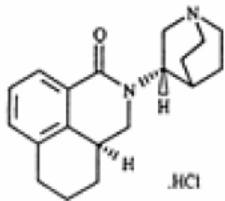
Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water and soluble in methanol.

CMC Assessment Section

Palonosetron hydrochloride injection is a sterile, clear, colorless, non pyrogenic, isotonic, buffered solution for intravenous administration. Palonosetron hydrochloride injection is available as 5 mL single (b) (4) vial or 1.5 mL single (b) (4) vial.

Each 5 mL vial contains 0.25 mg palonosetron base (b) (4), 207.5 mg mannitol, and sodium acetate trihydrate in water for intravenous administration. Each 1.5 mL vial contains 0.075 mg palonosetron base (b) (4), 62.25 mg mannitol, and sodium acetate trihydrate in water for intravenous administration.

The pH of the solution in the 5 mL and 1.5 mL vials is 4.5 to 5.5, Hydrochloric acid or sodium hydroxide may have been added to adjust pH.

Item	Information Provided in NDA
Proprietary name and established name	Palonosetron hydrochloride injection Satisfactory
Dosage form and route of administration	injection for intravenous administration Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	Yes Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each 5 mL vial contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, and sodium acetate trihydrate in water for intravenous administration. Each 1.5 mL vial contains 0.075 mg palonosetron base as hydrochloride, 62.25 mg mannitol, and sodium acetate trihydrate in water for intravenous administration. The pH of the solution in the 5 mL and 1.5 mL vials is 4.5 to 5.5, Hydrochloric acid or sodium hydroxide may have been added to adjust pH. Not satisfactory
Statement of being sterile (if applicable)	Yes
Pharmacological/ therapeutic class	Serotonin subtype 3 (5-HT ₃) receptor antagonist
Chemical name, structural formula, molecular weight	 <p>palonosetron hydrochloride 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 Molecular weight is 332.87. Satisfactory</p>
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	pH is 4.5 to 5.5 Satisfactory

CMC Assessment Section

Evaluation: Regulations require that quantitative information about inactive ingredients other than those used to adjust pH or osmolality is given for injectable drug products. Amount of sodium acetate trihydrate is not stated.

The “Description” section is not adequate.

#16: How Supplied/Storage and Handling

[Redacted] (b) (4)

Storage

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

Item	Information Provided in NDA
Strength of dosage form	0.25 mg/5 mL [Redacted] (b) (4) 0.075 mg/1.5 mL [Redacted] (b) (4) Satisfactory
Available units (e.g., bottles of 100 tablets)	carton containing 5 vials (0.25 mg), or carton containing 1 vial (0.075 mg) Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC 55111-788-19 (0.25 mg), or NDC 55111-788-07 (0.075 mg) Satisfactory
Special handling (e.g., protect from light)	Protect from freezing Protect from light Satisfactory
Storage conditions	Store at 20-25°C (68-77°F) [Redacted] (b) (4) [Redacted] Satisfactory
Manufacturer/distributor name (21 CFR 201.1(h)(5))	None, however it shows at the bottom of the package insert. Satisfactory

Evaluation: **The “How Supplied/Storage and Handling” section is adequate.**

Overall PI Evaluation:

The following items are deficient in the Prescribing Information:

- Section 11 (Description) does not list quantitative amount sodium acetate, as required for injectable drug products.

The Prescribing Information is **NOT ADEQUATE**.

CMC Assessment Section

2. Immediate container labels

The image of the label for 0.075 mg/1.5 mL vial is shown below:



Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Palonosetron hydrochloride injection. Palonosetron and Hydrochloride should be in the same line. Not Satisfactory
Dosage strength	0.075 mg / 1.5 mL Satisfactory
Net contents	N/A
“Rx only” displayed prominently on the main panel	Yes Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	Yes Satisfactory
Lot number and expiration date (21 CFR 201.17)	Yes Satisfactory
Storage conditions	Store at 20-25°C (68-77°F). [Redacted] (b) (4) [Redacted] Satisfactory
Bar code (21CFR 201.25)	Yes Satisfactory
Name of manufacturer/distributor	Mfd. By Gland Pharma Limited Satisfactory
And others, if space is available	Protect from light Satisfactory

The label for 0.25 mg / 5 mL vial tablet blister is very similar, except the strength declaration. The same comments apply.

Evaluation: Palonosetron and Hydrochloride should be in the same line in the label.

Both vial labels are not adequate.

3. Carton labeling

CMC Assessment Section

The image of the proposed carton for 0.075 mg/1.5 mL vial is shown below:



Item	Information Provided in NDA
Proprietary name, established name (font size, prominence)	Palonosetron hydrochloride injection. Palonosetron and Hydrochloride should be in the same line. Not Satisfactory
Dosage strength	0.075 mg / 1.5 mL Satisfactory
Net quantity of dosage form	Five single (b) (4) vials Satisfactory
"Rx only" displayed prominently on the main panel	Yes Satisfactory
Lot number and expiration date	Yes Satisfactory
Storage conditions	Store at 20-25°C (68-77°F). (b) (4)

CMC Assessment Section

	(b) (4)
	Satisfactory
Bar code (21CFR 201.25)	Yes Satisfactory
NDC number (21 CFR 207.35(b)(3)(i))	Yes Satisfactory
Manufacturer/distributor's name	Mfd. By Gland Pharma Limited Satisfactory
Quantitative ingredient information (injectables)	Yes Satisfactory
Statement of being sterile (if applicable)	None
“See package insert for dosage information”	Yes Satisfactory
“Keep out of reach of children” (Required for OTC in CFR. Optional for Rx drugs)	N/A

Evaluation: Although the statement of being sterile is not on the carton label, it is acceptable since it appears in the “Description” section of the Prescribing Information, as required by 21 CFR 201.57 (c)(12)(D). Also the carton for 0.25 mg / 5 mL vials has all the required information as listed above.

The only issue is the arrangement of the established name in the carton labels. “Palonosetron” and “Hydrochloride” should be in the same line.

Carton labels are not adequate.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The sponsor claims categorical exclusion from the Environmental Assessment based on 21 CFR 25.31(a).

Evaluation: The sponsor explains that that proposed drug product is an alternative to the approved drug product Aloxi. The proposed new drug will not be administered at a higher dosage level, for a longer duration, or for different indications than were previously in effect. No extraordinary circumstances exist. **ADEQUATE.**

III. List of Deficiencies

Label/labeling issues:

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

Palonosetron Hydrochloride Injection.
0.075 mg/1.5 mL and 0.25 mg/5 mL

(These will be addressed later during the labeling discussion with the sponsor)



CMC Assessment Section

IV. Attachment - Establishment Evaluation Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 203050/000	Sponsor:	DR REDDYS LABS LTD
Org. Code:	180		200 SOMERSET CORPORATE BLVD 7TH FL
Priority:	5		BRIDGEWATER, NJ 08807
Stamp Date:	03-JAN-2012	Brand Name:	ALOXI
PDUFA Date:	03-NOV-2012	Estab. Name:	
Action Goal:		Generic Name:	palonosetron hydrochloride
District Goal:	04-SEP-2012	Product Number; Dosage Form; Ingredient; Strengths	
			001; INJECTION; PALONOSETRON HYDROCHLORIDE; .075MG/1.5ML
			002; INJECTION; PALONOSETRON HYDROCHLORIDE; .25MG/5ML
FDA Contacts:	C. TRAN-ZWANETZ	Project Manager	(HFD-800) 3017963877
	B. KURTYKA	Review Chemist	3017961431
	M. KOWBLANSKY	Team Leader	3017961390

Overall Recommendation:	ACCEPTABLE	on 24-FEB-2012	by A. INYARD	(HFD-323)	3017965363
	PENDING	on 23-FEB-2012	by EES_PROD		
	PENDING	on 23-FEB-2012	by EES_PROD		

Establishment:	CFN: 9617755	FEI: 3002949085	(b) (4)
	DR. REDDY'S LABORATORIES LTD (b) (4)		
	RANASTHALAM MANDAL SRIKAKULAM, ANDHRA PRADESH, INDIA 532409		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	(b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-FEB-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN:	FEI: 3002647489	
	GLAND PHARMA LIMITED (b) (4)		
	INDIA		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	(b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-FEB-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

/s/

BOGDAN KURTYKA
08/10/2012

MOO JHONG RHEE
08/10/2012
Chief, Branch IV

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	203-050
Product name, generic name of the active, and dosage form and strength	Palonosetron HCl Injection 0.075 mg* / 1.5 mL; 0.25 mg* / 5 mL (b) (4)
Submission date	January 3, 2012 (eCTD 0000)
Applicant	Dr. Reddy's Laboratories
Medical Division	DGIEP
Type of Submission	505(b)(2) NDA
Biopharmaceutics Reviewer	Mark R. Seggel
Biopharmaceutics Lead	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?		X	Drug product is a solution administered by intravenous injection.
2.	Is the dissolution test part of the DP specifications?		X	
3.	Does the application contain the dissolution method development report?		X	
4.	Is there a validation package for the analytical method and dissolution methodology?		X	
5.	Does the application include a biowaiver request?	X		Biowaiver requested pursuant to 21 CFR 320.22(b)(1)
6.	Does the application include a IVIVC model?		X	
7.	Is information such as BCS classification mentioned, and supportive data provided?		X	
8.	Is information on mixing the product with foods or liquids included?		X	
9.	Is there any in vivo BA or BE information in the submission?		X	No clinical pharmacology studies were conducted by the applicant. This part of the submission will be reviewed by the Office of Clinical Pharmacology.

**PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW**

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
10.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
11.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	-	-	NA
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	X	-	Fileable
13.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	No comments for the Applicant

{See appended electronic signature page}

Mark R. Seggel
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

03/3/12
Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Supervisory Lead (acting)
Office of New Drug Quality Assessment

03/09/12
Date

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/s/

MARK R SEGCEL
03/21/2012

ANGELICA DORANTES
03/21/2012

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division: Division of Gastroenterology and Inborn Error Products
NDA: 203-050
Applicant: Dr. Reddy's Laboratories
Stamp Date: 1/3/2012
Review Date: 3/1/2012
PDUFA Date: 11/03/2012
Filing Meeting: 2/15/2012
Proposed Trademark: Not provided
Established Name: Palonosetron Hydrochloride Injection
Dosage Form: solution
Route of Administration: intravenous
Indication: nausea and vomiting associated with Chemotherapy

CMC Lead: Marie Kowblansky, PhD

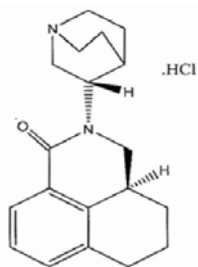
	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter		<input checked="" type="checkbox"/>

A. Summary

Palonosetron Hydrochloride Injection is intended for use in the prevention of nausea and vomiting in patients undergoing chemotherapy. The product is manufactured in two strengths, 0.25mg/5mL and 0.075mg/1.5mL, where the palonosetron (b) (4). Administration instructions call to intravenous administration and limit the dose to no more than 0.25 mg per day. This NDA is being filed as a 505(b)(2) application, with Aloxi (palonosetron hydrochloride) Injection (NDA 21-372) as the reference listed drug (RLD). There is no IND associated with this application.

Drug Substance

Palonosetron Hydrochloride



will be manufactured by Dr. Reddy's Laboratories in India. Although a brief overview of the CMC manufacturing process and controls is provided in the application, DMF 23590 is referenced for complete information regarding the drug substance manufacturing process, process controls, characterization, and impurities.

The drug substance specification includes testing for: description, identification by IR, HPLC, solubility, and chloride testing, optical rotation, chiral purity by HPLC, assay ((b) (4) %), identified and unidentified impurities (all of which conform to ICH recommendations), hydrochloride content, moisture, heavy metals, (b) (4) and residual solvents, as well as sterility, bacterial endotoxin, and bioburden testing. The proposed impurity limits conform to ICH qualification and identification thresholds.

Drug Product

Palonosetron Hydrochloride Injection is formulated as a solution to contain palonosetron hydrochloride, mannitol (b) (4) sodium acetate (b) (4), water for injection, sodium hydroxide or hydrochloric acid (for pH adjustment) (b) (4). With the exception of palonosetron hydrochloride, all components are compendial. The 0.075 mg/1.5 mL and 0.25 mg/5 mL strengths are respectively packaged in 2 mL and 5 mL USP Type-I glass vials and stoppered with (b) (4) rubber stoppers and sealed with Flip-Off seals. It will be manufactured at Dr. Reddy's in India. All excipients are compendial

The (b) (4) current product (both strengths) (b) (4) of reference listed drug (b) (4)

The reference drug contains citrate buffer instead of acetate buffer and also contains EDTA. Consequently, the applicant requests a waiver for conducting *in-vivo* bioequivalence studies. This request will be evaluated by the Biopharmaceutics reviewer.

The drug product is manufactured (b) (4) The sterile process and associated tests will be evaluated by the OPS Microbiology reviewer.

The product specification will include testing for description, clarity, pH, assay (HPLC), and identified and unidentified impurities. Acceptance limits conform to USP recommendations.

Six months of accelerated and 12 months of long term (room temperature) stability data have been submitted to support the proposed 24 month expiration dating period. Whether this extrapolation to 24 months is warranted will be determined as part of the full review of this NDA.

Established name: palonosetron hydrochloride, which is the USAN name

The applicant claims categorical exclusion from filing an environmental assessment on the basis of 21 CFR 25.31, the proposed product has the same indication and dosage as the reference drug; therefore it will not increase the use of this active moiety.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES.

The CMC reviewer for this NDA will be Dr. Bogdan Kurtyka.

The reviewer for the Biopharmaceutics information and the biowaiver will be Dr. Mark Seggel.

The sterile process and related sterility issues will be evaluated by the OPS Microbiology Group.

B. Critical issues for review

The proposed product (b) (4) the reference listed drug, with just some difference in excipients. The manufacturing process and controls that are described are standard for this type of product. There are no unusual issues that require special attention. The only obvious issue that will require closer attention is the label:

--Product strength is listed in terms of palonosetron (b) (4); the established name that is used in the labeling is the hydrochloride. Product labeling should be closely scrutinized to ensure that the basis for expressing the strength is clear from the product label.

C. Comments for 74-Day Letter – None

D. Recommendation – From the CMC perspective this application is fileable

Marie Kowblansky, PhD
CMC Lead

3/1/2012
Date

Moo-Jhong Rhee, PhD
Branch Chief

FILING CHECKLIST

NDA Number:	Supplement Number and Type:	Established/Proper Name:
203-050	original	Palonosetron hydrochloride (INN)
Applicant:	Letter Date:	Stamp Date:
Ferring Pharmaceuticals	December 30, 2010	

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			Not applicable

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 		√	Not applicable, drug product is packed in the manufacturing facility
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		√	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	√		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	√		For details NDA refers to DMF 23590
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		√	NDA refers to DMF 23590
14.	Does the section contain information regarding the characterization of the DS?	√		For details NDA refers to DMF 23590
15.	Does the section contain controls for the DS?	√		For details NDA refers to DMF 23590
16.	Has stability data and analysis been provided for the drug substance?	√		For details NDA refers to DMF 23590
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required; not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required; not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?	√		
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required; not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required; not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	√		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	√		Sterility assurance package is provided in the 3.2.P.3.5 Process Validation section

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		√	

{See appended electronic signature page}

Bogdan Kurtyka, Ph.D.
 CMC Reviewer
 Division of Pre-Marketing Assessment #
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Name of
 Branch Chief
 Division of Pre-Marketing Assessment #
 Office of New Drug Quality Assessment

Date

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

/s/

MARIE KOWBLANSKY
03/02/2012

MOO JHONG RHEE
03/02/2012
Chief, Branch IV