CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207963Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
This 505(b)(2) application is recommended for **Approval** in its present form from the OPQ perspective.

NDA 207963 (Resubmission)
Review # 2

Drug Name/Dosage Form	Palonosetron Hydrochloride Injection
Strength	0.25 mg palonosetron in 2 mL (0.125 mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Exela
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	N/A	
Drug Product	Thomas Paino	OMPT/CDER/OPQ/ONDP/DND PII/NDPBV
Process	N/A	
Microbiology	Stephen Langille	OMPT/CDER/OPQ/OPF/DMA/MABIII
Facility	Ebern Dobbin	OMPT/CDER/OPQ/OPF/DIA/IABII
Biopharmaceutics	Vidula Kolhatkar	OMPT/CDER/OPQ/ONDP/DB/BBII
Regulatory Business Process Manager	Truong Quach	OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Danuta Gromek-Woods	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. NDA 207963

2. REVIEW #: 2

3. REVIEW DATE: 25-Feb-2016

4. REVIEWER: Thomas C. Paino

5. PREVIOUS DOCUMENTS: See Review #1

6. SUBMISSION(S) BEING REVIEWED:

Supp. Document Number	Submit / Final Date	Supporting Document Category/Subcategory / Communication Function	Submission Type-Submission Number (Submission Classification)
18	09/15/2015	Resubmission/Class 2	Original-1 (Type 5- New Formulation or New Manufacturer)

7. NAME & ADDRESS OF APPLICANT:

Name: Exela Pharma Sciences
Address: 1245 Blowing Rock Blvd.
PO Box 818
Lenoir, NC 28645
Representative: Jonathan E. Sterling, Vice President
Telephone: 828-758-5474

8. DRUG PRODUCT NAME/CODE/TYPE:

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

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

10. PHARMACOL. CATEGORY: Antiemetic; antinauseant

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.25 (b)(4) mg/2 mL (0.125 mg/mL)

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

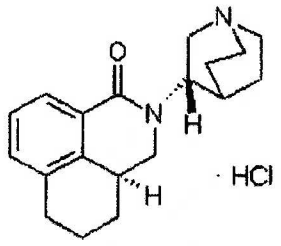
__√__ Not a SPOTS product

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

Nomenclature

INN: Palonosetron Hydrochloride
USAN: Palonosetron Hydrochloride
Chemical name: (3aS)-2-[(S)-I-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-l-oxo-1Hbenz[de] isoquinoline hydrochloride
CAS#: 135729-62-3 (palonosetron hydrochloride)
135729-56-5 (palonosetron)

Structure



Molecular formula: $C_{19}H_{24}N_2O \cdot HCl$
Molecular weight: 332.87 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFER-ENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	1	Adequate	Oct 20, 2015	----------
	V			1	Adequate	08/25/15	----------
	III			1	Adequate	9/25/12	----------
	II			1	Adequate	05/12/2015	From the ONDP perspective, this DMF (b) (4) is deemed adequate for approval of NDA 207963.

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	116583	Palonosetron Hydrochloride
NDA	021372	Aloxi® SOLUTION

18. STATUS:

ONDP:

CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biopharm	Approvable.	11-Mar-2016	Vidula Kolhatkar
Microbiology	Approvable.	15-Dec-2015	Stephen Langille

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The deficiencies noted in the CR letter dated 15-Jun 15, 2015 have been satisfactorily resolved per Microbiology review (Dr. Stephen E. Langille) and Biopharmaceutics Reviews (Dr. Vidula Kolhatkar), respectively.

The Office of Process and Facility had made an approval recommendation for the facilities involved in this application in the previous review cycle on June 15, 2015.

The labeling/labels issues are also satisfactorily resolved as of this review.

Therefore, this application is recommended for Approval from the OPQ perspective.

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

NA

II. Summary of Quality Assessments

This resubmission, dated 22-Sep-2015, is a response to deficiencies outlined in the Complete Response Letter dated 15-Jun-2015.

A. Drug Substance, palonosetron hydrochloride, Quality Summary

Refer to Review #1 in panorama dated 19-May-2015, prepared by Raymond Frankewich.

B. Drug Product Palonosetron Hydrochloride Injection Quality Summary

The Complete Response Letter, sent to the applicant on 15-Jun-2015, indicated the following major quality issues in the areas of Microbiology and Biopharmaceutics:

1. You have not provided an adequate description of the (b) (4) associated with the processing of the finished drug product. Provide the (b) (4) for the drug product (b) (4)
2. We cannot grant your request for a Biowaiver until the safety issues related to the hypotonicity of your product, as described above, are resolved.

The Quality Microbiology Reviewer, Dr. E. Stephen L. Langille, concludes that the applicant provided a satisfactory description of the (b) (4) and change control methodology for amending the established (b) (4). Thus, this application is recommended for approval from the Microbiology perspective.

Based on assessment of the drug product Reviewer, Mr. Tom Paino, labeling/labels issues are satisfactorily resolved.

In the previous review cycle, the Biopharmaceutics reviewer, Dr. Vidula Kolhatkar, concluded that biowaver could not be granted due to concerns related to the differences in osmolality between the NDA drug product and the listed drug. The proposed product differs from the listed product in that it does not contain (b) (4) mannitol, and disodium edetate (EDTA) and the palonosetron hydrochloride concentration is 2.5 times higher compared to the listed drug.

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 rationale is as follows:

- (b) (4)
- The pH of the proposed product (measured pH (b) (4)) is different than that of the listed product (measured pH 5.0). However, proposed product's pH range encompasses the normal pH range of blood ((b) (4)). Based on the buffer capacity of blood and total volume of administration, this is considered acceptable. Therefore, the difference in pH between the proposed and listed drug products is not expected to impact pharmacokinetics of the proposed product.
- Although mannitol is an osmotic diuretic that can affect kidney function, absence of small amount of mannitol (b) (4) mg) is not expected to affect palonosetron renal clearance.

In conclusion, as consistent with 21 CFR 320.24(b)(6), the FDA deemed adequate information supporting the relative bioavailability of Exela's proposed drug product to the listed drug and a scientific bridge has been established to the Agency's finding of safety and effectiveness for the listed drug. Thus, additional in vivo bioequivalence (BE) bridging study is not needed.

In conclusion, the applicant has adequately addressed the deficiency # 2 in the CR letter for the safety concerns and biowaver justification.

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	• 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
Maximum Daily Dose	
Alternative Methods of Administration	NA

C. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: Class 1
   - Drug Product: NA

2. Biowaivers/Biostudies
   - Biowaiver Requests: Yes, please see the Biopharmaceutics review
   - PK studies: N/A
   - IVIVC: N/A

D. Novel Approaches

E. Any Special Product Quality Labeling Recommendations

F. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Signature:

This 505(b)(2) application is recommended for **Approval** in its present form from the OPQ perspective.

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

Danuta E. Gromek-woods -S

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Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE: See Review #1

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT:

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:
This resubmission was submitted in response to previous Complete Response letter, dated June 15, 2015, which delineated two major product quality issues:

1. You have not provided an adequate description of the (b) (4) associated with the processing of the finished drug product. Provide the (b) (4) for the drug product (b) (4)
2. We cannot grant your request for a Biowaiver until the safety issues related to the hypotonicity of your product, as described above, are resolved.

The applicant responded to the Item #1 and Item #2, and Microbiology and Biopharmaceutics reviewers evaluated the response to each Item, respectively, and found them acceptable (see their reviews below), and therefore, this resubmission is recommended for approval from the drug product perspective.

Thomas C Paino
Reviewer, Branch V
DNDP II/ONDP

Moojhong Rhee -S
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Secondary Review Comments and Concurrence:
I concur with the Mr. Paino's assessment and his recommendation of approval of this application from the drug product perspective.

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

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ASSESSMENT OF THE PROCESS

N/A

ASSESSMENT OF THE FACILITIES

N/A

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation

Reviewer's Assessment:

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Secondary Review Comments and Concurrence:

ASSESSMENT OF THE BIOPHARMACUETICS

Applicant's Response to the CR letter:

In the previous review cycle (initial submission dated August 08, 2014), the Division of Biopharmaceutics (DB), agreed with the Medical Division's decision for the safety concerns on the differences in osmolality between the Applicant's proposed drug product and the listed drug. Therefore, it was concluded by DB that the biowaiver could not be granted. Please see Biopharmaceutics original review by Dr. Vidula Kolhatkar dated May 11, 2015.
FDA issued a complete response (CR) letter on 06/15/15.

To address the deficiency related to hypotonicity in the CR letter, the clinical division recommended the following in the action letter:
To address this deficiency, data can be provided from literature sources, nonclinical studies, or through review of intravenous products with comparable formulation characteristics. Particularly address the potential for hemolysis in patients with smaller blood volumes in whom the potential for hemolysis may be greater.

In addition, provide justification that the design (including sample size and choice of comparator) and results of Study EPS-2014-001 support that the tonicity and pH will not pose a significant safety risk.

NDA Resubmission (Dated 09/15/15): the Applicant conducted an in vitro hemolysis study with the proposed drug product, and submitted the study report. Dr. Tracy Behrsing reviewed these studies (Pharmacology/toxicology NDA review and evaluation February

19, 2016). Dr. Behrsing stated that the results of the in vitro hemolysis study with Palonosetron HCl Injection suggest that the proposed drug formulation is not expected to cause a clinically relevant hemolysis.

An internal meeting was also held between DB and the clinical team (Dr. Anil Rajpal and Dr. Aisha Peterson) on February 23, 2016. Dr. Aisha Peterson noted the following in her review related to safety and low osmolality of the proposed product:

Safety concerns of a hypotonic intravenous solution include injection site pain and hemolysis. Results of a local irritation study conducted in the first review cycle confirmed that this product does not present a safety concern related to local irritation. Similarly, the analysis of the results of the in vitro hemolysis study submitted in the current review cycle do not suggest that the hypotonic solution of the 2mL adult dose will result in clinically relevant hemolysis.

Dr. Peterson recommended approval for the proposed product (Clinical review by Dr. Aisha Peterson dated February 25, 2016).

Reviewer's Comment:
Based on the clinical review by Dr. Aisha Peterson, the Applicant has adequately addressed the safety concerns about the differences in osmolality between the Applicant's proposed drug product and the listed product.

In accordance with 21 CFR §320.22(a) the applicant requested a waiver of in vivo bioavailability/bioequivalence requirements for the proposed product. The request is based on 21 CFR §320.22(b). 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 proposed product differs from the listed product in that the proposed product does not contain (b) (4) mannitol, and disodium edetate (EDTA).

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 207963, the absence of (b) (4) mannitol, and EDTA in the formulation of the proposed drug product is not expected to impact the bioavailability of palonosetron following intravenous (IV) administration. The rationale is as follows:

(b) (4)

- The proposed product does not contain any buffer or pH adjuster. The pH of the proposed product (measured pH (b) (4)) is different than that of the listed product (measured pH 5.0). However, proposed product's pH range encompasses the normal pH range of blood ((b) (4)) while the listed product Aloxi's pH range is more acidic than human blood. Therefore, the pH associated with the proposed product is more physiologic than the listed drug.

  The applicant has stated that the total blood buffer value is 76.8 mEq/L for a change of one pH unit[3]. The proposed drug product has only palonosetron hydrochloride and water for injection. This does not affect the blood buffer or blood pH upon introduction of drug into systemic circulation. Based on the buffer capacity of blood and total volume of administration, this is considered acceptable. The difference in pH therefore, is not expected to impact pharmacokinetics of the proposed product[2, 3].

- Absence of mannitol in Exela's product is thus not expected to affect renal clearance of palonosetron. After a single IV dosing of 10 mcg/kg [^{14}C]-palonosetron, approximately 80% of the dose was recovered in the urine with palonosetron representing approximately 40% of the administered dose. As stated in Aloxi label, mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic (PK) parameters. Total systemic exposure increased by approximately 28% in severe renal impairment relative to healthy subjects. Dosage adjustment is not necessary in patients with any degree of renal impairment [4]. 5 mL Aloxi contains only (b) (4) mg mannitol. Therefore, although mannitol is an osmotic diuretic that can affect kidney function, absence of small amount of mannitol (b) (4) mg) is not expected to affect palonosetron clearance[5].

Recommended dosage for the proposed product and Aloxi is 0.25 (b) (4) mg administered intravenously. The same amount is mixed with normal saline prior to administration as a single dose over 30 seconds. This is expected to give comparable C_{max} from either Aloxi,

listed drug or the proposed product. Thus, the mean C_{max} (and so as to the mean AUC) of palonosetron, would be expected to be the same for a patient regardless whether the Aloxi, the listed drug or the proposed drug product is used.
Overall, in summary from biopharmaceutics perspective, the Applicant provided adequate justification that the differences in the formulation for the proposed product and the listed drug do not affect the PK performance of the proposed drug product compared to that of the listed drug product. The bioavailability of the product is expected to be comparable.

In conclusion, as consistent with 21 CFR 320.24(b)(6), the FDA deemed adequate information supporting the relative bioavailability of Exela's proposed drug product to the listed drug and a scientific bridge has been established to the Agency's finding of safety and effectiveness for the listed drug. Thus, additional in vivo bioequivalence (BE) bridging study is not needed.

Reviewer's Assessment:

Based on the overall studies and information submitted to this NDA and justification provided, the Applicant has adequately addressed the Product Quality point #2 in the CR letter for the safety concerns and also to the PK concerns due to the absence in EDTA, sodium acetate (b) (4) and mannitol.

Therefore, from the scientific point of view, the bioavailability of Exela's palonosetron IV Inj. drug product is acceptable and additional bridging BE study is not needed.

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[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.
[2] European Public Assessment Reports (EPAR) for ALOXI® (palonosetron hydrochloride) Injection
Clinical trial data of palonosetron hydrochloride published in Europe. It is stated that in Phase I and II trials were conducted with the formulation containing phosphate buffer (pH range 6.2 - 8.2) whereas the commercial formulation used in Phase III trial had citrate buffer (pH range 3.7 - 5.7). Despite the differences between the two formulations, a bridging BE study between the Phase I/II and Phase III formulations was not required by the EMA and bioequivalence of these two formulations was considered to be self-evident because both formulations were administered as aqueous solutions by IV route, and for the same duration (i.e., over 30 seconds), and the differences in excipients did not seem to affect bioavailability.
[3] A published article cites blood buffer value 76.8 mEq/L (Yale Journal of Journal of Biology and Medicine, 32: 378-389).
[4] Aloxi label
[5] To use mannitol as osmotic diuretic the following dosage is suggested for patients with marked oliguria or suspected inadequate renal function: a test dose of about 0.2 g/kg or 12.5 g as a 15 or 20% solution infused over a period of 3-5 minutes to test renal response before mannitol therapy is initiated. This dose is significantly higher than the mannitol administered with Aloxi ((b) (4) mg in 5 mL).

Reference for the test dose: Gerald K. McEvoy, Pharm.D., ed. 2016. AHFS Drug Information® - 58th Ed. Bethesda, MD. American Society of Health-System Pharmacists. ISBN-10: 1-58528-557-9, ISBN-13: 978-1-58528-557-0. ISSN: 8756-6028. STAT!Ref Online Electronic Medical Library. http://online.statref.com/Document.aspx?fxId=1&docId=976. 3/8/2016 9:34:18 PM CST (UTC -06:00).

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

NDA 207963 for Palonosetron hydrochloride injection, 0.125 mg/mL is recommended for approval.

Vidula Kolhatkar, Ph.D.
Branch II
Division of Biopharmaceutics/ONDP/OPQ
03/21/2016

Vidula R. Kolhatkar -S
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Date: 2016.03.22 09:09:58 -04'00'

Secondary Review Comments and Concurrence:

I Concur 03/21/16

Tien-Mien Chen, Ph.D.
Acting Biopharmaceutics Lead, BBII/DB/ONDP/OPQ

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ASSESSMENT OF MICROBIOLOGY

Applicant's Response to the CR letter:
The initial product quality microbiology review of NDA 207963 was completed on 18 May 2015. Because a complete response action was to be taken for this NDA, the following microbiology deficiency was provided to the applicant in the complete response letter:

> *Provide the* [redacted] (b) (4) *for the drug product* [redacted] (b) (4).

Exela Pharma provided a class 2 resubmission of NDA 207963 on 15 September 2015. In it, Exela stated that "A formal bulk [redacted] (b) (4) study will be executed as part of the prospective process performance qualification for Palonosetron Hydrochloride Injection"

The following information request was provided to the applicant on 11 November 2015.

> *We acknowledge your commitment to conduct bioburden and endotoxins studies on the bulk drug product* [redacted] (b) (4).

(b) (4) for the drug product (b) (4) should be established as per 21 CFR (b) (4). Provide the (b) (4) for the drug product (b) (4).

Exela provided a response on 24 November 2015 committing to limit the (b) (4) In addition, Exela will conduct studies to evaluate the bioburden (TAMC and TYMC), endotoxin, pH, and assay for the (b) (4) bulk held under static conditions for 24-96 hours. Based upon the results of these studies, Exela may (b) (4) the batch record. A (b) (4) bioburden limit of no more than (b) (4) CFU/mL was provided in the original application.

Reviewer's Assessment:

The applicant provided a satisfactory description of the (b) (4) change control methodology for amending the established (b) (4)

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

The drug product is recommended for approval from the standpoint of product quality microbiology.

Stephen E. Langille -S
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Stephen E. Langille, Ph.D.

Secondary Review Comments and Concurrence:

I concur.

John W. Metcalfe -A
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John W. Metcalfe, Ph.D.

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

1. PI

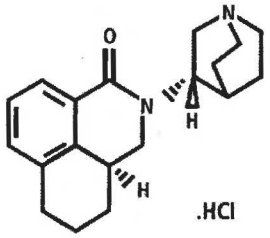
3 DOSAGE FORM AND STRENGTHS

Palonosetron Hydrochloride Injection is sterile, clear, and colorless:

- 0.25 mg palonosetron in 2 mL (0.125 mg/mL) in a single-dose vial

11 DESCRIPTION

Palonosetron Hydrochloride (b) (4) an antiemetic and antinauseant agent. It is a serotonin-3 (5-HT_3) 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- 1*H*benz[*de*]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O{\cdot}HCl$, 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, non-buffered, hypotonic solution for intravenous administration. Palonosetron HCl Injection contains no preservative or chelating agent. Palonosetron HCl Injection is available as 2 mL single-dosevial.

Each 2 mL vial contains 0.25 mg palonosetron base equivalent to XX mg palonosetron HCl, and water for intravenous administration.

The pH of the solution in the 2 mL vial is 6.5 to 8.5

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

NDC Number	Strength	Package
51754-0204-1	0.25 mg/2 mL (0.125 mg/mL)	1 vial/carton

Storage

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

17 PATIENT COUNSELING INFORMATION

(b) (4)

2. Labels

1) Container label

(b) (4)

2) Carton label

(b) (4)

Barcode
Rx Only

Conclusion:

The PI (#3, #11, #16, and #17) and labels for container and cartons are satisfactorily revised from the CMC perspective. The major difference from the first review cycle is the change of the established name, (b) (4) to '*palonosetron hydrochloride*'. This decision was based on the historical exception described in the CDER salt nomenclature policy.

Thomas C. Paino
Reviewer, Branch V
DNDP II/ONDP

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
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Date: 2016.03.22 08:58:10 -04'00'

I concur with the reviewer's assessment.

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

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: 2016.03.22 08:58:34 -04'00'

NDA 207963

Palonosetron Injection
0.125 mg/mL

Exela Pharma Sciences

Raymond P. Frankewich, Ph.D.

Review Chemist

Office of New Drug Products
Division of New Drug Products II
Branch V

CMC REVIEW
For the Division of Gastroenterology and Inborn Errors Products
(CDER/OND/ODEIII/DGIEP, HFD-180)

Table of Contents

CMC Review Data Sheet

1. NDA 207963

2. REVIEW #: 1

3. REVIEW DATE: 18-May-2015

4. REVIEWER: Raymond P. Frankewich, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	August 7, 2014
Amendment (BC)	December 31, 2014
Amendment (BC)	January 8, 2015 (labeling)
Correspondence (C)	March 4, 2015
Correspondence (C)	March 6, 2015
Amendment	March 31, 2015 (labeling)
Amendment	April 24, 2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Exela Pharma Sciences
Address:	1245 Blowing Rock Blvd. PO Box 818 Lenoir, NC 28645
Representative:	Jonathan E. Sterling, Vice President
Telephone:	828-758-5474

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name: Palonosetron Injection
c) Code Name/# (ONDP only): None
d) Chem. Type/Submission Priority (ONDP only):

- Chem. Type: 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antiemetic; antinauseant

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.125 mg/mL (0.25 (b) (4) mg/2 mL) as palonosetron base

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

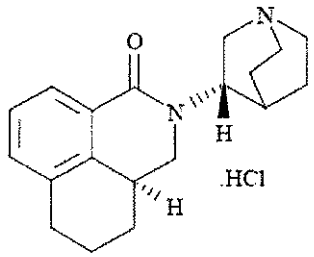
__√__ Not a SPOTS product

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

Palonosetron hydrochloride

Chemical name (IUPAC name): (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

Structural formula:



Molecular formula: $C_{19}H_{24}N_2O \cdot HCl$

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	May 8, 2015	Memo by R. P. Frankewich
	III			1	Adequate	October 7, 2005	Review by Jila Boal, Ph.D.*
	III			3	Adequate	June 6, 2011	Review by Josephine Jee

* - The LOA specified that the latest revision of the DMF was dated August 18, 2006. However, after review of the amendment dated August 18, 2006 and associated list of changes (dated October 9, 2006) it was determined that the conclusions of the review dated October 7, 2005 apply.

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
NDA		

18. STATUS:

ONDP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	April 7, 2015	Christina Capacci-Daniel
Pharm/Tox	NA		
Biopharm (Bioavailability)	Not Acceptable	May 2, 2015	Vidula Kolhatkar, Ph.D.
LNC	NA		
Methods Validation	N/A, according to the current ONDP policy		
DMETS	NA		
EA	Categorical exclusion (see review)		
Microbiology (Sterility)	Not Acceptable	May 18, 2015	Stephen Langille, Ph.D.

The CMC Review for NDA 207963

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has ***not*** provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

A final "Acceptable" recommendation from Office of Compliance for the manufacturing facilities has been made.

The information on the label/labeling currently is ***not*** completely resolved as of this review from the CMC perspective.

Therefore, from the CMC perspective, this NDA is ***not*** ready for approval at this time in its present form per 21CFR314.125(b)(1),(6) until above issues are satisfactorily resolved.

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

NA

II. Summary of CMC Assessments

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

(1) Drug Substance

****Throughout this review, the USAN name, palonosetron hydrochloride, is being used. However, per salt name policy, the established name will be presented as palonosetron. So when palonosetron is expressed for some reason, it actually represents palonosetron hydrochloride.***

The drug substance is palonosetron hydrochloride. This drug substance is (one of) the active ingredient(s) in two prescription drug products that are currently marketed, according to the Orange Book: Aloxi® (palonosetron HCl) Injection (0.25 mg/5 mL, 0.075 mg/1.5 mL), and Akynzeo® (netupitant and palonosetron) capsules (300 mg netupitant / 0.5 mg palonosetron) . According to the Orange Book, Aloxi® capsules, an oral dosage form approved in 2008 under NDA 22-233, has been discontinued.

Aloxi Injection has been marketed in the U. S. since 2003. Aloxi Injection (approved under NDA 21-372) is referenced as the Reference Listed Drug (RLD) for this 505(b)(2) application.

Palonosetron hydrochloride is described in USAN as an anti-emetic / antinauseant. In this application, palonosetron is indicated for the prevention of nausea and vomiting after / during moderately and highly emetogenic cancer chemotherapy treatments due to repeated courses (chemotherapy induced nausea and vomiting) (b) (4)

Palonosetron hydrochloride is a white to almost-white crystalline powder. It is sourced from (b) (4) the holder of Drug Master File (DMF) (b) (4).

(2) Drug Product

NOTE: the proposed proprietary name for this drug product is "Palonosetron Hydrochloride Injection". To comply with the USP Salt Naming Policy, the agency proposed the name "Palonosetron Injection". In this review the drug product is referred to as "Palonosteron Injection". In places where text has been copied from the NDA submission, the name of the drug product will appear as "Palonosetron Hydrochloride Injection".

The drug product consists of palonosetron hydrochloride dissolved in USP Water for Injection (WFI) at a concentration of 0.125 mg/mL. The drug product is (b) (4) The drug product is packaged in a 2 mL vial so that the amount of palonosetron supplied in one vial is 0.25 (b) (4) mg / (b) (4) as palonosetron hydrochloride).

(b) (4)

The palonosetron concentration of the listed drug product Aloxi® is 0.25 mg / 5 mL (0.05 mg/mL, as free base) or 0.075 mg / 1.5 mL (as free base), whereas Exela's formulation contains palonosetron with a concentration of 0.125 mg/mL (as free base).

The listed drug product Aloxi® contains mannitol (b) (4) disodium edetate (b) (4) and citrate (b) (4) in water for injection (solvent), whereas Palonosetron Injection proposed by this NDA contains water for injection as solvent (b) (4) This formulation contains no tonicity agent, no buffering agent, and no chelating agent, and Biopharmaceutics Review, dated May 2, 2015, noted that osmolarity is different from RLD and, therefore, the requested biowaiver is denied.

The drug product is packaged in a 2 mL USP Type I glass vial with a rubber stopper and an aluminum flip-off overseal. Sterility of the drug product is not deemed assured according to Microbiology Review dated May 18, 2015.

An expiration date of 24 months is requested for this drug product by the applicant. To justify, stability data through 18 months storage for three lots (b) (4) and 12 months storage for one lot (b) (4) have been provided in this NDA, and the proposed 24 month expiration date is considered acceptable.

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

Among the proposed indications for this drug product are Moderately and Highly emetogenic cancer therapy ("Moderately emetogenic" is defined as prevention of acute and delayed nausea and vomiting associated with initial and repeat courses; "Highly emetogenic" is defined as only the acute condition). This indication is also described as Chemotherapy Induced Nausea and Vomiting (CINV).

(b) (4)

The drug product is intended to be administered as a single IV dose. For CINV, the dose is 0.25 (b) (4) mg over 30 seconds, approximately 30 minutes before the start of chemotherapy. (b) (4)

C. Basis for Not-Ready for Approval Recommendation

21 CFR 314.125(b)(1)

- Microbiology Review recommends CR action due to sterility issues.
- Biopharm Review recommends CR action because the applicant's request for biowaiver cannot be granted due to different osmolarity of the proposed current formulation from the RLD.

21 CFR 314.125(b)(6)

- Labels and labeling issues have not been fully resolved from the CMC perspective.

(see the **List of Deficiencies**, p. 60)

III. Administrative

A. Reviewer's Signature:

Raymond P. Frankewich -S

Digitally signed by Raymond P. Frankewich -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300093657, cn=Raymond P. Frankewich -S
Date: 2015.05.18 12:36:41 -04'00'

Raymond P. Frankewich, Ph.D., DNDAPI, Branch I, OPQ

B. Endorsement Block:

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: 2015.05.19 12:50:25 -04'00'

Moo-Jhong Rhee, Ph.D., Branch Chief, DNDPII Branch V, OPQ

C. CC Block: entered electronically in Panorama

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

There were no significant changes in the exposed samples, compared to the unexposed. The (b) (4) appears to have no effect on the product.

Apparently due to an abundance of caution, the applicant has added the instruction "protect from freezing" to the package insert.

A APPENDICES

A.1 Facilities and Equipment (biotech only) NA

A.2 Adventitious Agents Safety Evaluation NA

A.3 Novel Excipients NA

R REGIONAL INFORMATION

R1 Executed Batch Records

Executed batch records are not provided. A batch record for the revised manufacturing process (non-executed) was provided in the amendment dated December 31, 2014.

R2 Comparability Protocols NA

R3 Methods Validation Package

NA. The drug substance is not a NME and the application does not meet the criteria of IQP 5105 for the submission of a methods validation package to FDA laboratories.

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

A. Labeling & Package Insert

The package insert reviewed in this section was submitted in the amendment dated March 31, 2014. It provides for the changes proposed in the amendment dated December 31, 2014.

1. Package Insert

(a) "Highlights" Section

PALONOSETRON INJECTION for Intravenous Use
Initial US Approval: 2003

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	"Palonosetron". There is no proprietary name. **Acceptable.**
Dosage form, route of administration	"Injection". **Acceptable.**
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (201.57(a)(8))	
Whether the drug product is scored	NA

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths

(b) (4)

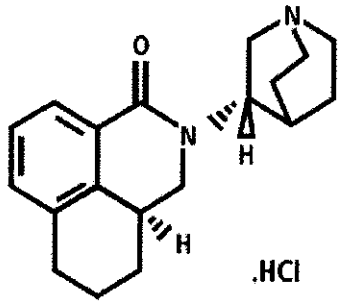
Item	Information Provided in NDA
Available dosage forms	"Injection". **Acceptable.**
Strengths: in metric system	0.25 mg (b) (4) is expressed. An equivalency statement for palonosetron hydrochloride should be in this statement (see below). **Acceptable.**
Active moiety expression of strength with equivalence statement (if applicable)	Equivalency statement has not been provided. See comment below. **Not Acceptable.**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	"single(b) (4) sterile, clear, colorless solution in (b) (4) vials". **Acceptable.**

The revised **Dosage Forms and Strengths** section reads as follows:

(b) (4)

#11: Description

Palonosetron (b) (4) 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-1Hbenz[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, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

Palonosetron Injection is a sterile, clear, colorless, non-pyrogenic, non-buffered, hypotonic solution for intravenous administration. Palonosetron Injection contains no preservative or chelating agent. Palonosetron Injection is available as 2 mL single use vial. Each 2 mL vial contains 0.250 mg palonosetron base as palonosetron hydrochloride, and water for injection for intravenous administration.

The pH of the solution in the 2 mL vials is (b) (4).

Item	Information Provided in NDA
Proprietary name and established name	"Palonosetron Injection" (established name). Product has no proprietary name. **Acceptable.**
Dosage form and route of administration	"Palonosetron Injection is a …solution for intravenous administration". **Acceptable.**
Active moiety expression of strength with equivalence statement (if applicable)	"Each 2 mL vial contains 0.25 (b) (4) mg palonosetron base as palonosetron hydrochloride" **Acceptable.**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	WFI is the only excipient. It is accounted for. **Acceptable.**

Statement of being sterile (if applicable)	Product is described as being sterile. **Acceptable.**
Pharmacological/ therapeutic class	"antiemetic and antinauseant agent". **Acceptable.**
Chemical name, structural formula, molecular weight	Information is provided. Editorial changes are made. **Acceptable.**
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	The pH of the solution is provided but it is incorrect. The correct value is 6.5 – 8.5. **Not Acceptable (** See below).

Evaluation: The following phrases need to be revised in the Description section.

- (b) (4)

  "Palonosetron Injection contains palonosetron hydrochloride which is an antiemetic and antinauseant agent."

- "Chemically, palonosetron hydrochloride is…": to

  "Palonosetron hydrochloride is…:"

  "The pH of the solution in the 2 mL vials is (b) (4)" to

  "The pH of the solution in the 2 mL vials is 6.5 – 8.5.

#16: How Supplied/Storage and Handling

(b) (4)

Storage

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

CMC Assessment Section

Item	Information Provided in NDA
Strength of dosage form	"0.25 (b) (4) mg/2 mL (b) (4) "Palonosetron" will be added for clarity. **Not Acceptable** (See correction below).
Available units (e.g., bottles of 100 tablets)	Single (b) (4) vials are not packaged in individual cartons (b) (4) **Not Acceptable** (See correction below).
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Place for NDC number is provided. **Acceptable** (See comment below).
Special handling (e.g., protect from light)	Instructions are provided to protect product from both freezing and light. **Acceptable.**
Storage conditions	USP storage statement is provided (although it does not reference USP). **Acceptable.**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	(b) (4) **Acceptable.**

Evaluation: (b) (4) in the How Supplied / Storage and Handling section should be revised as follows:

"Palonosetron Injection 0.25 (b) (4) mg/2 mL (b) (4) vial packaged (b) (4)

2. Immediate container labels

(b) (4)

Item	Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4) **Not Acceptable.**
Dosage strength	0.25 (b) (4) mg / 2 mL. **Acceptable.**
Net contents	"2 mL single-(b) (4) sterile vial". **Acceptable.**
"Rx only" displayed prominently on the main panel	"Rx Only" prominently displayed. **Acceptable.**
NDC number (21 CFR 207.35(b)(3)(i))	Space for NDC number provided. **Acceptable**
Lot number and expiration date (21 CFR 201.17)	Space is provided for lot number and expiration date. **Acceptable.**
Storage conditions	(b) (4) **Not Acceptable** (See comment below).
Bar code (21CFR 201.25)	Space for Bar code is provided. **Acceptable**
Name of manufacturer/distributor	(b) (4) **Acceptable.**
And others, if space is available	NA

Evaluation: The following comments should be sent to the applicant regarding both the vial and carton (see evaluation below) label:

(b) (4)

3. Carton labeling

(b) (4)

Item	Information Provided in NDA
Proprietary name, established name (font size, prominence)	(b) (4) **Not Acceptable.**
Dosage strength	0.25 (b) (4) mg / 2 mL. Acceptable.
Net quantity of dosage form	(b) (4) **Acceptable.**
"Rx only" displayed prominently on the main panel	"Rx Only" prominently displayed. Acceptable.
Lot number and expiration date	Space is provided for lot number and expiration date. **Acceptable.**
Storage conditions	(b) (4) . Not Acceptable (See comment above).
Bar code (21CFR 201.25)	Liocation of Bar code is provided. **Acceptable.**
NDC number (21 CFR 207.35(b)(3)(i))	Space for NDC number provided. **Acceptable.,**
Manufacturer/distributor's name	(b) (4) . **Acceptable.**
Quantitative ingredient information (injectables)	(b) (4) **Acceptable.**
Statement of being sterile (if applicable)	(b) (4) **Acceptable.**
"See package insert for dosage information"	This statement is not provided. **Not Acceptable** (See comment below).
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	NA

Evaluation: See evaluation above for vial label. The same comments apply for the carton label.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The applicant claims categorical exclusion from the requirements of an Environmental Impact Analysis statement, based on 21 CFR §25.31 (a) which states that action on an NDA is excluded if the action does not increase the use of the active moiety.

III. List Of Deficiencies to be Communicated

A. Regarding CMC:

a. Provide the [redacted] for the drug product [redacted].

b. The requested biowaiver cannot be granted due to the different osmolarity of the proposed formulation from the RLD.

B. Regarding label/labeling

1. PI

a. The Dosage Forms and Strengths section,

- "Injection: 0.25 mg [redacted] 2 mL [redacted]

should be revised to

"Injection: 0.25 mg palonosetron [redacted] 2 mL, [redacted]

b. Description section:

- Revise "[redacted]
  "Palonosetron Injection contains palonosetron hydrochloride which is an antiemetic and antinauseant agent."
- Revise "Chemically, palonosetron hydrochloride is…": to, *"Palonosetron hydrochloride is…:"*
- Revise "The pH of the solution in the 2 mL vials is [redacted]" to, *"The pH of the solution in the 2 mL vials is 6.5 – 8.5.*

c. How Supplied/Storage and Handling section:

- Revise [redacted]

  "Palonosetron Injection 0.25 [redacted] mg/2 mL [redacted] single-[redacted] vial packaged [redacted]

2. Labels

- Change the name [redacted]

(b) (4)

[redacted]

IV. Attachments

EES Reports

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet

1. OMPQ Reviewer: Christina Capacci-Daniel, PhD

2. NDA/BLA Number: NDA 207963
   Submission Date: August 15, 2014
   21st C. Review Goal Date: April 15, 2015
   PDUFA Goal Date: June 15, 2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	*To be determined*
Established or Non-Proprietary Name (USAN) and strength:	Palonosetron Hydrochloride Injection
Dosage Form:	Injection

4. SUBMISSION PROPERTIES:

Review Priority :	Standard
Applicant Name:	Exela Pharma Sciences LLC
Responsible Organization (OND Division):	DGIEP

II. Application Detail

1. INDICATION: Prevention of nausea and vomiting after/during moderately and highly emetogenic cancer chemotherapy treatments. (b) (4) .

2. ROUTE OF ADMINISTRATION: i.v. injection

3. STRENGTH/POTENCY: 0.125 mg/mL

4. Rx/OTC DISPENSED: ☒Rx ☐OTC

5. ELECTRONIC SUBMISSION (yes/no)? YES

6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		☑		
2.	Breakthrough Therapy Designation		☑		
3.	Orphan Drug Designation		☑		
4.	Unapproved New Drug		☑		
5.	Medically Necessary Determination		☑		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		☑		
7.	Rolling Submission		☑		
8.	Drug/device combination product with consult		☑		
9.	Complex manufacturing		☑		
10.	Other (e.g., expedited for an unlisted reason)		☑		

III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	☑		356h
12.	Do all sites indicate they are ready to be inspected (on 356h)?	☑		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	☑		356h
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	☑		Testing responsibilities are described broadly (release, stability) or exactly (container closure integrity)
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	☑		
		☑		
			☑	Approved sterile injectable products

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		☑	

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?		☑	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	☑		
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	☑		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):	☑ Not Applicable		

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		☑	• DMF (b) (4) received a 31 item deficiency letter in 11/2012; updated DMF still appears deficient • No manufacturing process development in DMF • No process parameters or controls in DMF (no CPPs, PARs/NORs, nor IPCs) • "In process controls" consist of API (b) (4) specifications • Critical to control content (b) (4) in final product

(b) (4)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		☑	(b) (4)

(b) (4)

3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

- The Palonosetron HCl API DMF lacks substantive manufacturing process control information.

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

- There are no outstanding compliance issues. The facility has had 3 NAI and 2 VAI drug inspections since 2010.

Additional information not covered above

- No additional items.

Manufacturing Facilities Chart (generated 19 Sept 2014):

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Comment
(b) (4)								
EXELA PHARMA SCIENCES	3008563008	ATL	USA	DP manufacture, DP release & stability testing, DP packaging & labeling	(b) (4)		SUBMITTED TO DO (10-Day)	Recently inspected

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) **YES**
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. • No KTMs are currently warranted. If sufficient process details are received and a PAI is triggered for the API facility, a KTM or pre-inspection briefing will be provided.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) **NO**
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL
(DARRTS)

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

/s/

CHRISTINA A CAPACCI-DANIEL
10/02/2014

MAHESH R RAMANADHAM
10/02/2014