

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207963Orig1s000

SUMMARY REVIEW

Division Directory Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD. MPH. Deputy Director for Safety Division of Gastroenterology and Inborn Errors Products ODE III CDER/FDA
Subject	Division Director Summary Review
NDA #	207963
Applicant	Exela Pharma Sciences, LLC
Date of Re-Submission (third review period)	June 22, 2016
PDUFA Goal Date	August 22, 2016
Proprietary Name / Non-Proprietary Name	Palonosetron Hydrochloride Injection
Dosage Form(s) / Strength(s)	Solution for Intravenous Injection, 0.125 mg/mL
Applicant Proposed Indication(s)/Population(s)	Current re-submission: Chemotherapy-Induced Nausea and Vomiting (CINV): <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
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	Chemotherapy-Induced Nausea and Vomiting in <u>Adults</u> Palonosetron Hydrochloride (HCl) Injection is indicated for: <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

Executive Summary:

Excela Pharma Sciences, LLC submitted an amendment to New Drug application (NDA # 207963) dated August 7, 2014 for Palonosetron Hydrochloride (HCl) Injection, 0.125 mg/mL. This application was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Previously this application was reviewed by the Division of Gastroenterology and Inborn Errors Products (DGIEP) and was given a Complete Response on June 15, 2015.

The applicant responded to the deficiencies on September 22, 2015. Based upon the review of that amendment, it was determined that a Tentative Approval be granted. The action letter was sent on March 22, 2016.

“It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the package insert, text for the patient package insert) and submitted labeling (carton and immediate container labels submitted and received March 14, 2016 and March 17, 2016).”

“The listed drug upon which your application relies is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.”

On June 22, 2016 DGIEP received an amendment which constituted a complete response to the action letter. The outstanding issue was related to a pending patent infringement law suit, which has since been resolved. The 505(b)(2) team has verified that this.

We have reviewed this ammendment, and have determined that there are no new issues or outstanding deficiencies, and have concluded that this application be approved for the use of Palonosetron HCl Injection in adults for:

- 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.

The professional labeling was agreed upon during the previous review cycle, and is attached to the approval action letter.

For further details regarding the review of this application, refer to my summary review from the previous cycle which is attached to this memo (3/22/2016).

ATTACHMENT #1

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick, MD. MPH. Deputy Director for Safety Division of Gastroenterology and Inborn Errors Products ODE III CDER/FDA
Subject	Division Director Summary Review
NDA #	207963
Applicant	Exela Pharma Sciences, LLC
Date of Re-Submission (second review period)	September 22, 2015
Date of Original Submission	August 7, 2014
PDUFA Goal Date	March 22, 2016
Proprietary Name / Non-Proprietary Name	Palonosetron Hydrochloride Injection
Dosage Form(s) / Strength(s)	Solution for Intravenous Injection, 0.125 mg/mL
Applicant Proposed Indication(s)/Population(s)	Current re-submission: Chemotherapy-Induced Nausea and Vomiting (CINV): <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
Action/Recommended Action for NME:	Tentative Approval
Approved/Recommended Indication/Population(s) (if applicable)	Chemotherapy-Induced Nausea and Vomiting in <u>Adults</u> Palonosetron Hydrochloride (HCl) Injection is indicated for: <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

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Aisha P Johnson

Pharmacology Toxicology Review	Tracy Behrsing
OPQ Review	Lead: Danuta-Gromek-Woods Drug product- Thomas Paino Microbiology- Stephen Langille Facility- Ebern Dobbin Biopharmaceutics- Vidula Kolhatkar
Clinical Pharmacology Review	Sandhya Apparaju
OPDP	Metta Patel
CDTL Review	Anil Rajpal
OSE/DMEPA	Sherly Abraham
DMPP	Karen Dowdy
DPMH	Amy Taylor, Miriam Dinatale
Other	Previous Summary Review (15 JUNE 2015) Joyce Korvick

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA= Division of Medication Error Prevention and Analysis
DMPP= Division of Medical Policy Programs
DPMH= Division of Pediatric and Maternal Health
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

This 505(b)(2) application proposes a higher concentration of palonosetron hydrochloride than the currently approved listed drug product, Aloxi (palonosetron hydrochloride). Key differences of the proposed palonosetron hydrochloride product from Aloxi are the absence of disodium edetate (b)(4) citrate (b)(4) and mannitol (b)(4). Based upon review of the clinical safety study and in vitro hemolysis study, these differences are not expected to effect the efficacy or safety, or the pharmacokinetics of palonosetron.

For parenteral solutions, *in vivo* bioavailability/bioequivalence may be self-evident and a waiver of *in vivo* studies may be granted if they contain the same active and inactive ingredients in the same concentration. 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), FDA can rely on any other approach deemed adequate to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products. Specifically for this NDA, the difference in palonosetron concentration and the absence of buffer, mannitol, and EDTA in the formulation is not expected to impact the bioavailability of palonosetron following intravenous (IV) administration. Thus, the relative bioavailability of Exela's proposed product compared to the listed drug and a scientific bridge has been established to the Agency's finding of safety and effectiveness for the listed drug. Consequently, additional *in-vivo* bioequivalence (BE) bridging study is not needed.

This proposed product is indicated only for use in chemotherapy induced nausea and vomiting in adults. Possible safety risks associated with this new formulation may be related to "off-label" use in pediatrics or adult patients which may result in exposing patients to approximately twice the dose that is currently recommended for Aloxi for the prevention of chemotherapy induced nausea and vomiting (CINV) in adults. However, Exela has adequately bridged to the Agency's finding of safety and effectiveness for Aloxi to support approval of the proposed product. These findings are described in the approved labeling for Aloxi. It is known that increased exposure with palonosetron does not prolong the QT interval, and therefore potential concerns related to cardiac toxicity have been addressed. A thorough QT study was performed in adults (see Aloxi label) and the results did not show QT prolongation at the doses studied. The highest dose studied was 2.25 mg of palonosetron. Exela's product is presented as a single use 0.25 (b)(4) mg/2 mL (as base) compared to Aloxi which is available as 0.25 mg/5 mL (as base) for use in adults with CINV. If an error of delivering 2.5 times the dose was made, the resulting amount of palonosetron hydrochloride that would be delivered (0.625 mg) would be significantly lower than that studied in the Through QT study (see Aloxi label). In addition, if this new product were inadvertently administered to children, based on the pharmacokinetics of palonosetron in children compared to adults, the safety margin is adequate, (details in section 8 of this review).

The potential for adverse events related to the hypotonicity of the proposed product was evaluate. First, the clinical study EPS-2014-001 compared the potential for local irritation for that of the proposed product to Alxoi. No significant differences were noted. Secondly, the sponsor submitted an in vitro study for the potential risk of hemolysis. Based on that data and the calculations regarding the dilution factor in the human blood volume for adults and

children, we have concluded that there is an ample safety margin. Thirdly, the administration instructions tell the clinician to flush the line before and after administration. For CINV, patients receive intravenous drugs via a central line. The volume of the flush with normal saline would improve the tonicity of the drug product delivered as described in this review. Regarding the pH of the formulation, while different than Aloxi, it approximates the normal human blood pH. Finally, both professional and carton and container labeling should be adequate to distinguish these single use products meant to provide the complete dose to adult patients with CINV.

Therefore, based on the considerations from biopharmaceutics, clinical reviews, and medication error and prevention analysis, we conclude that this product is approvable.

Regulatory Recommendation:

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the package insert, text for the patient package insert, carton and immediate container labels).

The listed drug upon which this application relies is subject to a period of patent protection and therefore final approval of this application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

Exela's application contains certifications to each of the patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by this manufacture, use, or sale of, this drug product under this application ("Paragraph IV certifications").

Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be brought prior to the expiration of forty-five days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. Exela notified us that they complied with the requirements of section 505(b)(3) of the Act.

In addition, Exela notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against them with respect to patent 8,518,981 and 8,598,218 in the United States District Court, District of Delaware (Case 1:14-cv-01444-GMS). Therefore, final approval cannot be granted at this time (refer to tentative approval letter: March 22, 2016)

2. Background

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.

On August 7, 2014, Exela Pharma Sciences, LLC submitted a 505(b)(2) NDA to provide a new strength (0.125 mg/mL) of palonosetron from the Reference Listed Drug, Aloxi (NDA 21372) (original submission). A Complete Response letter was sent to Exela dated June 15, 2015.

This submission is a complete response from the applicant. It was received September 22, 2015. This is the second review cycle for Palonosetron Hydrochloride Injection.

This 505(b)(2) application relies, in part, on the Agency's finding of safety and efficacy of ALOXI Injection (NDA 21372, Helsinn Healthcare SA).

ALOXI (palonosetron hydrochloride) is a serotonin-3 (5-HT₃) receptor antagonist and has the following indications listed in the professional labeling:

INDICATIONS AND USAGE

1.1 Chemotherapy-Induced Nausea and Vomiting in Adults

ALOXI is indicated for:

- 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

1.2 Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients Aged 1 month to Less than 17 Years

ALOXI is indicated for prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy.

1.3 Postoperative Nausea and Vomiting in Adults

ALOXI is indicated for prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period, ALOXI is recommended even where the incidence of postoperative nausea and/or vomiting is low.

During this review cycle the applicant is seeking approval of the CINV indication only for adult patients. The Applicant believed that dosing error concerns were

(b) (4)

(b) (4)

(b) (4)

(b) (4)

adequate carton, container and professional labeling, the risk of medication error would be significantly reduced and has been determined to be acceptable.

The formulation of this product is different from the listed drug product in that it has different inactive ingredients, has a significantly different osmolality and has a higher concentration. Aloxi is currently marketed in the following concentrations:

- 0.25 mg (free base) per 5 mL (concentration: 0.05 mg/mL, 50 mcg/mL)
- 0.075 mg (free base) per 1.5 mL (concentration: 0.05 mg/mL, 50 mcg/mL)

The concentration proposed in this application for Palonosetron Hydrochloride Injection is 0.25^(b)₍₄₎ mg/2 mL (as base) (concentration: 0.125 mg/mL, 125 mcg/mL); which is 2.5 times the concentration of Aloxi.

In their resubmission dated September 22, 2015, Exela removed the Postoperative Nausea and Vomiting indication and the respective recommended dosing regimen to mitigate any potential for dosing errors. Exela believed that dosing error concerns were related to the product having two different indications and dosing regimens for this single strength product.

The following deficiencies are listed in the Complete Response Letter:
“CLINICAL

1. You did not provide sufficient information to establish the safety of the proposed formulation of your drug product. You have not established that the hypotonicity of your drug product will not result in clinically relevant hemolysis.

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.

2. You have not provided adequate information to establish that your proposed concentration would not increase the potential for dosing errors with palonosetron. To address this deficiency, conduct a Human Factors study to characterize the risks of confusion and dosing errors between the currently marketed concentration of palonosetron (0.05 mg/mL) and your proposed concentration ((0.125 mg/mL), and to demonstrate that your proposed strategies to address the identified risks mitigates the potential for error.

PRODUCT QUALITY

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.”

This review will focus, primarily, on the unresolved issues from the first review cycle including the final labeling review.

3. Product Quality

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. 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. The pH of the listed drug product is 4.5 to 5.5, whereas the pH range of the proposed drug product is 6.5 - 8.5. Finally, the listed drug contains the following inactive ingredients: mannitol (b) (4) disodium edetate (b) (4) citrate (b) (4) and water for injection. The Applicant’s proposed formulation has zero osmolality (0 mOsm/kg), and does not contain any excipients, such as buffers, tonicity agents, preservatives, or chelating agents.

Palonosetron HCl Injection is available as 2 mL single-dose vial. Each 2 mL vial contains 0.25 mg palonosetron base equivalent to 0.28 mg palonosetron HCl, and water for intravenous administration.

Table 1 Compares the Exela product with the approved Aloxi formulations.

Table 1: Side-by-Side Comparison of Exela’s Palonosetron Hydrochloride and the Reference Listed Drug

	Exela’s Palonosetron Hydrochloride (palonosetron hydrochloride) Injection	ALOXI® (palonosetron hydrochloride) Injection (RLD)
Active Ingredient	Palonosetron Hydrochloride	Palonosetron Hydrochloride
Strength(s)	0.125 mg/mL (as base)	0.05 mg/mL (as base)*
Configuration/label	0.25 (b) (4) mg/2 mL (as base)	0.25 mg/5 mL (as base) or 0.075 mg/1.5 mL (as base)
Excipients	(b) (4)	Mannitol Disodium edetate Citrate buffer
Solvent	(b) (4)	Water for Injection , USP
Dosage Form	Injection, solution	Injection, solution
Route of administration	Intravenous	Intravenous
(b) (4)		

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.” (This satisfactorily addresses the Product Quality deficiency # 1 of the CR letter).

Based on assessment of the drug product Reviewer, Mr. Tom Paino, Labeling/labels issues are satisfactorily resolved (see labeling section below).

Biopharmaceutics:

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.

As noted above, the proposed product differs from the listed product in that the proposed product does not contain any buffer, mannitol, and disodium edetate (EDTA).

Although the criteria for a bio waiver under 21 CFR 320.22(b)(1) is not fully met, based on 21 CFR 320.24(b)(6), FDA can rely on any other approach deemed adequate to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products. Specifically for this NDA, the difference in palonosetron concentration and the absence of buffer, mannitol, and EDTA in the formulation is not expected to impact the bioavailability of palonosetron following intravenous (IV) administration. Thus the relative bioavailability between the proposed product and listed drug is expected to be comparable and is sufficient to establish a bridge to the Agency's finding of safety and effectiveness for the listed drug. Consequently, an additional in-vivo bioequivalence (BE) bridging study is not needed.

The rationale supporting our review of this issue follows as listed in the OPQ review (review #1 second cycle):

- EDTA is used in the listed drug product (b) (4)



Please refer to CMC review by Dr. Raymond P. Frankewich dated May 19, 2015 for additional details. Absence of EDTA would not be expected to alter the pharmacologic activity of the product.¹

- 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 unit². 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. From a clinical standpoint, the difference in pH therefore, is not expected to impact pharmacokinetics of the proposed product.³

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 A published article cites blood buffer value 76.8 mEq/L (Yale Journal of Journal of Biology and Medicine, 32: 378-389).

³ We note that, although not necessary for approval of this product, our conclusion is consistent with experience regarding Aloxi in Europe. European Public Assessment Reports (EPAR) for ALOXI® (palonosetron

- 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 [¹⁴C]-palonosetron, approximately 80% of the dose was recovered in the urine with palonosetron representing approximately 40% of the administered dose⁴. As stated in the 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.⁵ From a clinical point of view, 5 mL Aloxi contains only (b) (4) mg mannitol. Therefore, although mannitol is an osmotic diuretic that can affect kidney function, absence of a small amount of mannitol (b) (4) mg) is not expected to affect palonosetron renal clearance.⁶

“The recommended dosage for the proposed product and Aloxi is 0.25 (b) (4) mg administered intravenously. The same amount of dose is mixed with normal saline prior to administration as a single dose over 30 seconds. This is expected to give the same C_{max} from either Aloxi, listed drug, or the proposed product. Thus, the mean C_{max} of palonosetron is expected to be the same for a patient regardless whether the Aloxi, the listed drug or the proposed drug product is used”.

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

Overall OPQ Summary:

The summary from the OPQ review regarding the outstanding review issues from the second cycle review #2 follow below:

“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.”

hydrochloride) Injection. Clinical trial data of palonosetron hydrochloride published in Europe. It is stated that in Phase I and II trials (b) (4)

Despite the (b) (4) a bridging BE study between the Phase I/II and Phase III formulations was not required by the EMA and bioequivalence of (b) (4) formulations was considered to be self-evident because (b) (4) 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

⁴ Aloxi labeling, Section 12.3 Pharmacokinetics, Elimination

⁵ Aloxi labeling, Section 8.6 Renal Impairment, available at

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021372s0201bl.pdf

⁶ 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 (b) (4) % 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).

The applicant provided a satisfactory description of the (b) (4) (b) (4) and change control methodology for amending the established (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. The rationale is as follows:”

- EDTA is used in the listed drug product (b) (4) (b) (4). Based on stability data, absence of EDTA does not seem to have an effect on stability of the proposed product. Therefore, the bioavailability of the proposed product is not expected to change during the labeled expiration dating period.
- 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 biowaiver justification.”

“The Office of Process and Facility had made an approval recommendation for the facilities involved in this application in the (b) (4) review cycle on June 15, 2015.”

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

- The only major difference from the first review cycle is the established name, palonosetron hydrochloride. It was decided that (b) (4) (b) (4) ”

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

I concur with the OPQ findings and recommendations. There are no outstanding CMC issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

In the original submission there were no nonclinical studies submitted. Under the Class 2 Resubmission, the applicant submitted an *in vitro* hemolysis study to evaluate the hemolytic potential of Palonosetron HCL Injection in human blood.

The reviewers state that “In this study, although the mean percent lysis following treatment with Palonosetron HCL Injection exceeded that of the vehicle and untreated controls, the maximum mean percent lysis observed with the test article was $\leq 1.5\%$ and at least 6 times lower than that observed for the positive control (Triton X-100). Therefore, the results of this study suggest that the test article is not expected to cause clinically relevant hemolysis.”

“Overall, there are no nonclinical safety issues for the drug substance based on the Agency’s previous determination of safety of palonosetron. In addition, from a nonclinical perspective, the results of the *in vitro* hemolysis study with Palonosetron HCL Injection suggest that the proposed drug formulation is not expected to have a hemolytic potential.”

I concur with the Nonclinical Pharmacology reviewer’s conclusions.

5. Clinical Pharmacology

There were no clinical pharmacology studies submitted for this application in either the first or second review cycle. Issues regarding potential “bioequivalence” are discussed in the OPQ section above. The clinical pharmacology reviewer found this resubmission acceptable.

I concur with the Clinical Pharmacology reviewer’s conclusions.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because palonosetron is not an antimicrobial agent.

7. Clinical/Statistical-Efficacy

There were not clinical efficacy studies conducted or submitted by the applicant. This 505(b)(2) application relies on the Agency’s findings of efficacy for the currently approved product ALOXI® (palonosetron hydrochloride) Injection, (NDA 021372) held by Helsinn Healthcare SA.

8. Safety

Overall, for the currently approved Aloxi product, there are three potentially serious side effects of note: hypersensitivity (anaphylaxis), serotonin syndrome (mostly seen with concomitant use of other serotonergic drugs), and the potential for QT prolongation in the class of 5-HT₃ receptor antagonists.

This 505(b)(2) application relies, in part, on the Agency's findings of safety for the currently approved product ALOXI® (palonosetron hydrochloride) Injection, (NDA 021372) held by Helsinn Healthcare SA, and a clinical safety study, *in vitro* hemolysis study and other literature.

The applicant submitted Study EPS-2014-001: A double blinded, randomized, single dose, parallel local irritation pilot study of intravenous administration of Palonosetron Hydrochloride 0.25 mg/ 2 mL Injection of Exela Pharma., USA with 0.9% Sodium Chloride Injection, USP, 2mL of [REDACTED]^{(b) (4)} in healthy, adult, human male and/ or female study participants under fasting condition. This is the only safety study conducted by the applicant for this proposed product. In addition to monitoring local irritation of this intravenous formulation, the applicant also monitored the study patients' clinical status, adverse events and performed clinical laboratory investigations.

The study is a double-blind, randomized, parallel, local irritation pilot study in which 32 healthy adult subjects were randomized 1:1 to receive the palonosetron or placebo control. The study included a 28-day screening period and a 10-day treatment period. Eligible subjects from the screening period were admitted to the study site the evening prior to dosing and underwent an overnight fast of at least 10 hours. Subjects were randomized to receive a single dose of either test or control, administered over 30 seconds, and were then monitored as per the schedule described in the protocol. Patients were discharged from the study site 48 hours post-dose and returned for subsequent assessments (72, 96, 120, 144, 168, 192, 216 and 240 hours post dose) on an outpatient basis.

The during the first review cycle the clinical reviewer found the comparator arm acceptable for testing the primary objective (Laurie Muldowney).

The reviewer had the following concerns regarding the safety evaluations:

“Patients were observed thoroughly for injection site reactions, and patients were monitored closely following injections for clinical symptoms associated with hemolysis. The laboratory assessment was insufficient to assess for hemolysis. Peripheral blood smears were not completed and LDH levels were not completed, for example. The frequency of relevant lab work that was completed (e.g., hemoglobin, hematocrit, bilirubin) was insufficient to detect subclinical hemolysis in the study, as labs were drawn prior to infusion and on day 10 only.”

“There were no incidents of phlebitis reported more than 4 hours post-dose in subjects receiving either test or control drug. There were no deaths, serious adverse events, or discontinuations due to adverse events during the study. One subject in each treatment arm reported one adverse event (AE), and these AEs were mild in intensity and resolved at the end of the study. There were no clinically significant changes in laboratory parameters, vital signs, or electrocardiograms. “

The reviewer concluded:

“While no safety signals were observed in the completed clinical study, in the absence of sufficient clinical or nonclinical data supporting the safety of the proposed drug product, there is no basis upon which to recommend approval of this product.”

Finally, the reviewer pointed to a concern regarding the potential for increased risk of hemolysis if this product were it to be used in patients with smaller fluid volumes (eg pediatric patients). The applicant has only requested the adult indication in this application. The clinical reviewer points out that based on the Aloxi dosing for pediatric patients with CINV a maximum dose per body weight could result in the infusion of 12 mL of hypotonic solution. This issue will need to be resolved prior to an approval in the pediatric population.

During the second review cycle, the medical reviewer commented on the issues regarding the potential risks hemolysis due to the osmolarity, differences in pH, and differences in concentration particularly related to off label dosing in pediatric populations. (Aisha P Johnson)

Hemolysis

In guidance, FDA recommends that sponsors who propose to use excipients intended for injectable use consider conducting an in vitro hemolysis study performed at the intended concentration for IV administration to determine the hemolytic potential.⁷ In accordance with this recommendation, Exela conducted a hemolysis study in human blood. Exela evaluated all four NDA submission stability lots of the Exela product, 0.125 mg/mL. Eight concentrations of the drug product in vehicle control were evaluated ranging from 0.098 mcg/mL to 12.5 mcg/mL. The highest concentration represents a 10 percent dilution in blood (chosen to address the potential for hemolysis in patients with smaller blood volumes). The hemolysis results at any concentration for all four lots were similar to the vehicle control. Therefore from a nonclinical perspective, the study results suggested that the Exela product is not expected to have hemolytic potential.

Considering that the use of an isotonic normal saline flush in intravenous tubing prior to delivering the Exela product intravenously, any risk of hemolysis should be additionally reduced. In Section 2.2 (Instructions for Intravenous Administration) of the Exela product’s labeling recommends, when applicable, flushing the line with normal saline before and after administration of the product to ensure complete dosing and to avoid drug incompatibilities. The tonicity of blood plasma is approximately 285-295 mOSM/L (an isotonic solution). The 2 mL dose of the Exela product will effectively be diluted in an isotonic saline solution (308 mOSM/L). Typically, the flush volume for indwelling catheters is 10 mL. If two 10 mL flushes are used, the resulting tonicity for the admixture (the Exela product and normal saline) entering the blood would be about 280 mOSM/L, which is approximately isotonic.

As noted above, Exela also completed a local irritation study in healthy volunteers to address potential safety concerns related to the hypotonicity, primarily to assess the local irritation by

⁷ FDA Guidance for Industry, Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, May 2005, available at <http://www.fda.gov/ohrms/dockets/98fr/2002d-0389-gdl0002.pdf>.

intravenous injection of the Exela product, 0.25 mg/ 2 mL compared with 0.9% Sodium Chloride Injection. The secondary objective of this study was to assess the relative safety and tolerance of the drug product. The results of this study demonstrated that the Exela product was well-tolerated locally

The reviewer concluded that the Exela application sufficiently addressed safety concerns relating to the Exela product's hypotonicity (osmolarity).

pH:

In general, pH differences can have the potential to cause safety concerns,; however, the Exela product's pH does not raise such concerns. The Exela product's pH is 6.5-8.5 and encompasses the normal pH range of blood ((b) (4)), while Aloxi's pH range (4.5 – 5.5) is more acidic than human blood. Hence, the pH associated with the Exela product is in fact more physiologic than Aloxi, and the Exela product's different pH did not raise safety concerns.

Concentration and Cardiac Repolarization:

The Aloxi sponsor conducted and submitted a thorough QT trial in 2007. The effect of palonosetron on QTc interval was evaluated in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) in 221 healthy subjects at doses up to 2.25 mg. The package insert includes this information as well as listing QTc prolongation as an infrequently reported adverse reaction (1%) in the clinical trials for Aloxi.⁸ Exela has adequately bridged to the Agency's safety findings including those related to QTc prolongation.

If a healthcare provider did, in fact, mistakenly use the Exela product in place of Aloxi, a patient would receive 2.5 times the indicated dose. In Aloxi's pediatric clinical trials, the highest dose studied was 20 micrograms/kilogram (mcg/kg) (the approved pediatric dose). In Aloxi's adult clinical trials, palonosetron was shown to be well tolerated at doses up to 90 mcg/kg.⁹ The safety profile of Aloxi is similar in adult and pediatric patients.¹⁰ Therefore, given that adult doses up to 90 mcg/kg were tolerated in adults, we expect that a 50 mcg/kg dose (2.5 times the indicated dose) in pediatric patients would be similarly well tolerated.

Although not necessary for approval of this product, we note our conclusions are consistent with nonclinical studies conducted on Aloxi. Studies of Aloxi in neonatal/juvenile rats and juvenile dogs provide additional confirmation that the risk of adverse events from potential overdose of palonosetron in pediatric patients is expected to be minimal. In the Aloxi studies conducted in rats, palonosetron was administered subcutaneously at doses ranging from 5000 to 25000 mcg/kg/day. In dogs, palonosetron was administered intravenously at doses ranging from 1000 to 6000 mcg/kg/day. 5000 mcg/kg was the tolerated dose in juvenile rats and 6000 mcg/kg was the tolerated dose in juvenile dogs. These doses are 250 and 300 times the recommended pediatric dose (20 mcg/kg), respectively. Even if a pediatric patient received

⁸ Aloxi labeling, section 12.2 Pharmacodynamics

⁹ Aloxi Labeling, NDA 021372 (approved on Sept. 18, 2014), section 10 (Overdosage).

¹⁰ Aloxi Labeling, NDA 021372 (approved on Sept. 18, 2014), section 8.4 (Pediatric Use).

2.5 times the recommended dose, these studies suggest a safety margin of more than a 100-fold.¹¹

Overall Safety: The medical officer commented that:

“The safety update provided with the current submission included data from recently published clinical studies and trials reported in the medical literature from January 2013 to August 2015 for ALOXI. The search to support this safety update included the Pubmed database and Google engine. The search terms used included: “palonosetron + adverse events”, “palonosetron + deaths”, “palonosetron + anaphylaxis”, “palonosetron + serotonin syndrome”, “palonosetron + case reports”, “palonosetron + safety”, and “palonosetron + QTc”. The Pubmed database was filtered for clinical trials and nonclinical studies separately.”

“No safety signals were identified that are not already included in palonosetron labeling. During this period, there were no reported deaths attributed to dosed palonosetron in any reported trials. There are no serious AEs reported that require further evaluation or specific monitoring. And these data do not suggest that anything other than continued routine postmarket surveillance is necessary at this point.”

Potential for Medication Dosing Error:

The Applicant is proposing a new strength for this product while the active ingredient, dosage form, and route of administration are the same as the listed product. Aloxi is currently approved for chemotherapy-induced nausea and vomiting (CINV) and post-operative nausea and vomiting (PONV). The adult dose for CINV is 0.25 mg as a single dose (delivery of entire 5-mL vial) and a pediatric dose of 20 mcg/kg (max 1.5 mg) as a single dose. The dose for PONV is 0.075 mg as a single intravenous dose (delivery of entire 1.5-mL vial). Exela is proposing an indication for CINV at a single dose of 0.25 mg. Because the strength of the proposed palonosetron is higher than what is currently approved for Aloxi, there was concern about the risk of dosing errors.

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. One significant addition in ^{(b) (4)} lettering on the principle display panel was made:

“^{(b) (4)}”

Among several other changes the statement “^{(b) (4)}” was made to accurately describe the correct usage of this product in single patient as a single injection. Their recommendations were conveyed to the Applicant and the changes were made. This was acceptable to DMEPA. (See section 12 of this review for complete list of recommendations)

I agree with the conclusions regarding adequate information which will mitigate the risk of dosing errors and there are no outstanding issues that preclude approval. Also, I agree that there are no new safety issues for palonosetron hydrochloride raised in this review, and no new clinical studies for safety are necessary. Finally, I agree that there is a margin of safety if

¹¹ Aloxi (NDA 21372) Pharmacology/Toxicology Review,
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-372_Alox.cfm.

adults or children would inadvertently receive an increased dose due to medication dosing error. There are no issues that are unresolved that preclude approval.

9. Advisory Committee Meeting

This is not an NME and therefore no Advisory Committee Meeting was held.

10. Pediatrics

The Applicant is not proposing a new active ingredient, a new dosage form, a new dosing regimen, or a new route of administration. Therefore, as per Section 505B of the Food, Drug and Cosmetic Act, the Sponsor acknowledges that the Pediatric Research Equity Act (PREA) does not apply to this application and therefore the Applicant has requested a full waiver of pediatric studies.

The DPMH Review noted the following regarding inclusion of pediatric information in the labeling:

- "Information on pediatric dosing, safety, pharmacokinetics, and a description of the pediatric studies supporting pediatric use is protected by the exclusivity awarded to the innovator Aloxi®. Therefore, this information cannot be included in labeling for this 505(b)(2) product."
- "Once the pediatric information is no longer protected, the specific language for the CINV indication, which is in the Aloxi® labeling, can be added to this product's labeling."

Concern was raised that the hypotonicity of the formulation may cause a safety concern in pediatric patients if this product is used off-label in pediatric patients. During the second review cycle the DPMH reviewers considered the results from the in vitro hemolysis study and the calculations of potential dosing based on the recommended dosing in the Aloxi labeling.

Dr. Johnson (in consultation with Dr. Behrsing) provided the following calculations:

“The highest concentration tested in the hemolysis study represented a 10% dilution. Given that Aloxi, the reference drug, has a pediatric indication, it is important to address the potential for off-label use of palonosetron hydrochloride in pediatric patients. To address this concern, the ratio of palonosetron hydrochloride drug volume to total blood volume (TBV) of pediatric patients was studied. These ratios were compared to the 1:10 (10%) dilution studied in the hemolysis study. The calculated dilution ratios of drug volume:TBV were approximately 1:500 for all pediatric age groups using weight data from CDC growth charts. It should be noted that the average pediatric dose volume ranges from 0.7 mL (1 month old dose) to a maximum volume of 12 mL.”

Table 2. Pediatric Dose/Volume Estimates and Calculated TBV Dilution¹²

Age	Weight*	Dose [‡] (20 mcg/kg)	Drug Volume [§] (0.125 mg/mL)	Average Total Blood Volume [#] (mL)	Dilution [†]
1 month	4.4 kg	0.088 mg	0.7 mL	350	1:500
6 months	6.4 kg	0.13 mg	1 mL	500	1:500
9 months	7.4 kg	0.14 mg	1.1 mL	600	1:545
6 years	16 kg	0.32 mg	2.6 mL	1120	1:430
10 years	26 kg	0.52 mg	4.2 mL	1820	1:433
16 years	50 kg	1.0 mg	8.0 mL	3500	1:437
		MAX DOSE 1.5 mg	MAX VOLUME 12 mL		

Table above is taken from the Clinical Review by Aisha Johnson

*Weight based on CDC growth charts, 5th percentile average of boys and girls

[#]Total Blood Volume estimated using approximation to Nadler's equation (80 mL/kg until 1 year, then 70 mL/kg)

[‡]Dose (in mg) calculated as Weight X .020 mg/kg

[§]Drug volume (in mL) calculated as follows: Dose (in mg) / 0.125 mg/mL

[†]Dilution of 1: X calculated as follows: X = Average Total Blood Volume / Drug Volume

The clinical reviewer concluded the following:

"When compared to the 1:10 dilution of the hemolysis study, the calculated dilution of approximately 1:500 (for pediatric and adult populations) provides reassurance that the potential for clinically relevant hemolysis is low and does not preclude approval of palonosetron hydrochloride."

DPMH concluded: "The 1:500 dilution compared to the 1:10 dilution in the in vitro study provides reassurance that significant hemolysis should not occur if this product is administered to pediatric patients. The hypotonicity of this product does not represent a safety concern if the product is administered off-label in pediatric patients."

I agree with these conclusions and recommendations.

11. Other Relevant Regulatory Issues

- *Exclusivity or patent issues of concern*

The application is cleared for tentative approval because a 30 month stay began on 10/20/2014 and has not yet expired. The stay is in effect because the NDA holder filed a lawsuit within 45 days of receiving notice on 10/20/2014.

¹² http://www.cdc.gov/growthcharts/data/who/grchrt_boys_24lw_100611.pdf and <http://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf>

- *Office of Scientific Investigations (OSI) Audits:* No clinical site inspections or OSI clinical inspections were involved in this NDA. The OPQ Office of Process and Facilities team made an approval recommendation for the facilities involved in this application in the previous review cycle (June 15, 2015).
- *Financial Disclosure;* deemed adequate by the clinical reviewer.

12. Labeling

Prescribing Information

- **INDICATIONS AND USAGE section:**

1.1 Chemotherapy-Induced Nausea and Vomiting in Adults

Palonosetron Hydrochloride (HCl) Injection is indicated for:

- 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
- Given that this single use dosage form has been developed to deliver the adult dose recommended for CINV in adults (b)(4)
his response is considered adequate to address that CLINICAL deficiency #2, along with additional labeling regarding the strength of the product as recommended by DMEPA. The request for a Human Factors study is therefore no longer needed.
- *I agree with this conclusion.*

- **DOSAGE AND ADMINISTRATION section:**

2.1 Recommended Dosage

Chemotherapy-Induced Nausea and Vomiting

The recommended adult dosage of Palonosetron HCl Injection is 0.25 mg administered as a single intravenous dose over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy.

- *I agree with this dosage based on the biopharmaceutics and clinical evaluation that this product would deliver a similar exposure to that of Aloxi.*

- **PEDIATRICS section:**

The DPMH review from the first cycle recommended changes to the following sections and as a result the specific changes were incorporated into the approved label attached to the tentative approval letter (March 22, 2016):

“Palonosetron HCl labeling has been updated to comply with the PLLR. A review of the literature for relevant data revealed no new data with palonosetron HCl use in pregnant or lactating women. DPMH has the following recommendations for palonosetron HCl labeling:

Pregnancy, Section 8.1

The “Pregnancy” subsection of palonosetron HCl labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” subsections.

Lactation, Section 8.2

The “Lactation” subsection of palonosetron HCl labeling was formatted in the PLLR format to include the “Risk Summary” subsection.”

The DPMH review from the second cycle recommended the following labeling:

8.4 Pediatric Use

This product has not been approved for use in pediatric patients for prevention of chemotherapy-induced nausea and vomiting.

The reviewers provided the following rationale: “Information on pediatric dosing, safety, pharmacokinetics, and a description of the pediatric studies supporting pediatric use is protected by the exclusivity awarded to the innovator Aloxi®. Therefore, this information cannot be included in labeling for this 505(b)(2) product. Including a statement that safety and effectiveness have not been established for pediatric patients for the CINV indication would not be a true statement. Safety and effectiveness have been established for pediatric CINV in Aloxi® and would also be established for use in this palonosetron product without additional pediatric studies if the pediatric indication was not protected. Stating that (b) (4) is a true statement and is an alternative statement as allowed under the regulations. DPMH recommends using the more general indication of “chemotherapy-induced nausea and vomiting” in order to avoid the possibility of including protected information in the labeling. Once the pediatric information is no longer protected, the specific language for the CINV indication, which is in the Aloxi® labeling, can be added to this product’s labeling.”

I agree with this recommendation and it has been added to the professional labeling.

Other Labeling

• *Carton and container labeling*

DMEPA review of labeling and carton container recommended wording that is intended to make the labeling clear regarding the higher concentration of this product compared to Aloxi. It was incorporated into the final labeling and is listed below.

1. Add a cautionary statement (b) (4) to the principal display panel that this product is (b) (4) See package insert for complete instructions.”

2. To mitigate the risk of confusion with the reference drug’s strength and subsequent dosing errors, we recommend revising the statement of (b) (4)

(b) (4)

3. Increase the prominence of the established name by increasing the font size.
4. As currently presented, the NDC number is located [REDACTED] (b) (4) the carton labeling. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling, in accordance with 21 CFR 207.35(3)(i). Relocate the NDC number from the side panel to the top third of the principal display panel.
5. As currently presented, there are [REDACTED] (b) (4) Rx only statements on the side panel. Please move one statement to the bottom right corner of the principal display panel [REDACTED] (b) (4).
6. Add a usual dosage statement to the side panel. For example, “Usual dose: See prescribing information”.
7. Remove the trailing zero from the strength presentation (0.25 mg/2 mL) to avoid misinterpretation of the product strength.
8. Delete the [REDACTED] (b) (4) statement since the proposed adult dosage for this formulation is the entire vial (0.25 mg).
9. Revise the [REDACTED] (b) (4) statement to “2 mL single dose sterile vial” since the term “single dose” accurately describes the correct usage of this product in single patient as a single injection.

On March 4, 2016 additional comments were sent to the applicant.

1. We recommend bolding the cautionary statement, [REDACTED] (b) (4) located on the Principal Display Panel, to ensure that this important information is not overlooked by health care providers.
2. Relocate the “Rx only” statement, currently on the side panel, to the Principal Display Panel.

All changes were satisfactorily incorporated into the labeling.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not deemed necessary for this product.

- Other Postmarketing Requirements and Commitments

No postmarketing studies were deemed necessary for this product.

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JOYCE A KORVICK
03/22/2016

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JOYCE A KORVICK
08/22/2016