

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207963Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	March 22, 2016
<b>From</b>	Anil Rajpal, MD, MPH, Clinical Team Leader Division of Gastroenterology Products
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/ BLA #</b>	NDA 207963
<b>Applicant</b>	Exela Pharma Sciences, LLC
<b>Date of Submission</b>	September 22, 2015
<b>PDUFA Goal Date</b>	March 22, 2016
<b>Proprietary Name / Established (USAN) names</b>	Palonosetron Hydrochloride Injection
<b>Dosage forms / Strength</b>	Solution for Intravenous Injection, 0.125 mg/mL
<b>Proposed Indication</b>	Chemotherapy-induced Nausea and Vomiting (CINV) - prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer (MEC) chemotherapy - prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer (HEC) chemotherapy
<b>Recommended Action:</b>	Tentative Approval

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## 1. Introduction

A Complete Response (CR) Letter was sent by the Division on June 15, 2015. This resubmission, received September 22, 2015, is a complete response to that letter, and represents the second review cycle for Palonosetron Hydrochloride Injection, a 5-HT<sub>3</sub> antagonist.

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

In the current submission, the Applicant is proposing the following indication in adults:

- Chemotherapy-Induced Nausea and Vomiting (CINV):
  - 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

(b) (4)

The proposed palonosetron formulation is intended to be therapeutically equivalent to ALOXI. Pursuant to 21 CFR §320.22(b)(1), the Applicant requested a biowaiver for the bioavailability/bioequivalence (BA/BE) requirement.

In the first review cycle, the Division determined that safety concerns related to the hypotonicity of the proposed product (discussed later in this CDTL review) precluded granting a biowaiver. In addition, there were CMC deficiency items identified in the first review cycle.

The primary emphasis of this memorandum is on the issues to be resolved in the current review cycle.

## 2. Background

### 2.1 Regulatory History

#### Overview

For regulatory activities prior to the first cycle submission, see the clinical review by Dr. Laurie Muldowney (DARRTS 15 June 2015).

The table below provides an overview of the regulatory activity of Palonosetron Hydrochloride Injection after the first cycle submission.

**Table 1. Pertinent Regulatory History of Palonosetron Hydrochloride Injection**

Date	Event
August 7, 2014	Applicant submitted the original NDA to the FDA for review.
June 15, 2015	FDA issued a Complete Response Letter (CRL) to the Applicant.
September 23, 2015	Applicant submitted their formal response to the deficiencies outlined in the CRL. This submission is the subject of the current review.

Above summarized from the Clinical Review by Aisha Peterson Johnson

For additional details of the regulatory history, see the Clinical Reviews by Laurie Muldowney and Aisha Peterson Johnson.

**First Review Cycle**

A Complete Response (CR) Letter was sent to the Applicant on June 15, 2015, outlining the reason for the CR action as follows:

“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.

## REGULATORY

1. It appears that Helsinn and Roche received notice under 21 CFR 314.52. With respect to any other owner(s) of the patent(s) that are the subject of the certification or the representative designated by the owner to receive notice, please submit to FDA adequate documentation of receipt of notice, or re-notify the relevant recipients and submit to FDA adequate documentation of receipt of notice. You did not submit a return receipt or letter acknowledging receipt by the person(s) provided notice. See 21 CFR 314.52. We note that FDA did not agree to another form of documentation in advance.”

### **Documents from First Review Cycle**

Review documents from the previous review cycle that were relied on by this reviewer included the following:

- Pharmacology/Toxicology Review by Tracy Behrsing, dated May 11, 2015
- Clinical Review by Laurie Muldowney, dated June 15, 2015
- Division of Pediatric and Maternal Health - Pregnancy and Lactation Labeling Review by Miriam Dinatale, dated April 29, 2015
- Biopharmaceutics Review by Vidula Kolhatkar, dated May 11, 2015

Correspondence from the previous review cycle cited by this reviewer consisted of the following:

- Complete Response Letter sent to Exela Pharma Sciences, LLC. dated June 15, 2015

## **2.2 Current Submission**

The NDA resubmission was received on September 22, 2015. It was classified as a six-month resubmission with a PDUFA deadline of March 22, 2016. No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines have all written review documents. The primary review documents relied upon were the following:

- (1) Clinical Review by Aisha Peterson Johnson, dated February 25, 2016
- (2) Pharmacology/Toxicology Review by Tracy Behrsing, dated February 19, 2016
- (3) Office of Pharmaceutical Quality Chemistry Manufacturing and Controls (CMC) Review (Application Technical Lead Danuta Gromek-Woods) dated March 22, 2016 which incorporates the following disciplines:

- (a) Drug Product (Thomas Paino)
  - (b) Microbiology (Stephen Langille)
  - (c) Facility (Ebern Dobbin)
  - (d) Biopharmaceutics (Vidula Kolhatkar)
- (4) Division of Medical Policy Programs (DMPP) Patient Labeling Review by Karen Dowdy, dated February 23, 2016
- (5) Clinical Pharmacology Review by Sandhya Apparaju, dated February 23, 2016
- (6) Labeling Reviews:
- (a) Division of Medication Error Prevention and Analysis (DMEPA) Label and Labeling Review by Sherly Abraham dated January 19, 2016 and Addendum dated March 21, 2016
  - (b) Office of Prescription Drug Promotion (OPDP) Review of Package Insert (PI) and Carton/Container Labeling by Meeta Patel, dated February 17, 2016
  - (c) Joint Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) Review of Patient Labeling: Patient Package Insert by Meeta Patel and Karen Dowdy, dated February 23, 2016
  - (d) Division of Pediatric and Maternal Health (DPMH) Labeling Review dated March 2, 2016

The reviews should be consulted for more specific details of the current application.

This memorandum summarizes selected information from the review documents, with primary emphasis on the issues to be resolved in the current review cycle.

### 3. CMC

#### 3.1 Initial Review Cycle

The deficiencies identified were from the Microbiology and Biopharmaceutics disciplines (see Quality CR items #1 and #2 in Section 2.1 of this CDTL Review). Below, an overview of CMC issues is provided followed by the conclusions/recommendations of the Microbiology and Biopharmaceutics disciplines.

#### **Overview of CMC Issues:**

The following summary of the CMC issues from the first review cycle is taken from the Clinical Review by Laurie Muldowney:

"A comparison of the ingredients in Exela's Palonosetron Hydrochloride Injection, 0.125 mg/mL with Helsinn Healthcare SA's ALOXI® (palonosetron hydrochloride) Injection is shown in **Table 2** below.

**Table 2: Side-by-Side Comparison of Exela’s Palonosetron Hydrochloride and the Reference Listed Drug**

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



The active ingredient concentration of the Exela product is 0.125 mg/mL (as base), compared to ALOXI® which contains 0.25mg/5 mL (as base) or 0.075 mg/1.5 mL (as base). Exela’s formulation contains no Mannitol<sup>(b) (4)</sup> disodium edetate<sup>(b) (4)</sup> or citrate<sup>(b) (4)</sup>.<sup>(b) (4)</sup> sodium hydroxide and hydrochloric acid as pH adjusters<sup>(b) (4)</sup>. These are commonly used excipients as pH control agents and are generally recognized as safe (GRAS).<sup>(b) (4)</sup>

**Reviewer Comments:**




*While the pH of the final drug product appears appropriate, the lack of tonicity agent results in a hypotonic solution, which may pose a safety risk (i.e., hemolysis) for patients with low blood volume and/or if a larger volume of drug product is administered. While this product will only be indicated in adults, it is likely that it will be used off label in pediatrics. Pediatric dosing is weight based and in some situations will result in a larger dose administered. Furthermore, ALOXI® is indicated down to 1 month of age. Infants have blood volumes substantially less than adults, which could potentially lead to hemolysis. Data is needed to support the use of a hypotonic injection in this context.*

*The Applicant’s product is a higher concentration than the RLD. The Sponsor of the RLD (Helsinn Healthcare) submitted a citizen petition on 13May2015 that this*

would result in medication errors. Based on preliminary review of the issues raised and discussion with DMEPA, we have determined that the introduction of a higher concentration has the potential to cause dosing errors. DMEPA noted that post-marketing evaluations of errors with other drug products has identified a risk for error with introduction of new concentrations. For example, FDA has received post-marketing reports of medication errors between 2 morphine oral solution drug products (20mg/mL and 20mg/5mL), some of which resulted in death. DMEPA recommends further assessment, including Human Factors testing, to characterize the risk of confusion and dosing errors between the currently marketed concentration of palonosetron (0.05 mg/mL) and the proposed concentration (0.125mg/mL) and to demonstrate that the Applicant's proposed strategies to address the identified risks mitigates the potential for error."

### **Microbiology Review**

The Microbiology Reviewer's comments and identified deficiency item were the following:

- **Comments:** It is noted that the biological indicator used (b) (4)  

- **Deficiency Item:** Provide the (b) (4)  
for the drug product (b) (4).

### **Biopharmaceutics Review**

The Biopharmaceutics Reviewer's comments and identified deficiency item were the following:

- **Comments:** "Biopharmaceutics review is focused on the evaluation of the requested information to support the biowaiver request. The Division of Biopharmaceutics is in agreement with the Medical Division's decision for the concerns on the differences in osmolality between the Applicant's proposed drug product and the RLD."
- **Deficiency Item:** "From the Biopharmaceutics perspective, the proposed biowaiver request could not be granted since the proposed drug product and RLD are considered different in osmolality. Therefore, NDA 207963 could not be recommended for approval."



The CMC deficiencies identified were sent to the Applicant in the CR Letter (see Section 2.1 of this CDTL Review).

### 3.2 Second (Current) Review Cycle

The Applicant's response to each of the CR items and the CMC Reviewers' conclusions are summarized below.

#### **Item #1**

CMC CR Item #1 was:

1. You have not provided an adequate description of the [REDACTED] (b) (4) of the finished drug product. Provide the p [REDACTED] (b) (4) for the drug product [REDACTED] (b) (4).

#### **a. Microbiology (Stephen Langille)**

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

#### **Item #2**

CMC CR Item #2 was:

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.

#### **a. Biopharmaceutics (Vidula Kolhatkar)**

##### Background:

The CMC Review provided the following regulatory background:

“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.”

Difference from Listed Drug Product:

The CMC Review explained that “The proposed product differs from the listed product in that the proposed product does not contain (b) (4) mannitol, and disodium edetate (EDTA).”

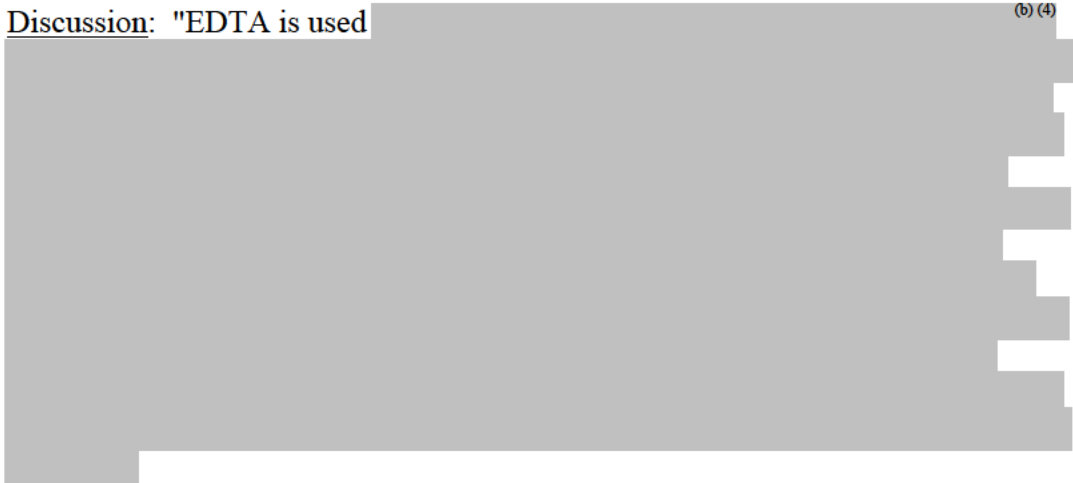
Approach to Establish Bridge Between the Proposed and Listed Drug Products:

The CMC Review stated that “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 administration.”

Detailed Rationale for Absence of (b) (4) Mannitol, and EDTA not Affecting PK:

- EDTA: The following is taken from the CMC Review:

➤ Discussion: “EDTA is used (b) (4)



➤ Conclusion: “Absence of EDTA would not be expected to alter the pharmacologic activity of the product<sup>1,2</sup>.”

Footnotes 1 and 2 from the CMC Review are shown below:

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. (b) (4)

(b) (4)  
a bridging BE study between the Phase I/II and Phase III formulations was not required by the EMA and bioequivalence of these (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."

- Buffer: The following is taken from the CMC Review:

- Discussion: "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<sup>3</sup>. The proposed drug product has only palonosetron hydrochloride and water for injection. This does not affect the blood buffer or blood pH upon introduction into systemic circulation."

Footnote 3 from the CMC Review is the following:

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

- Conclusion: "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<sup>2, 3</sup>."

- Mannitol: The following is taken from the CMC Review:

- Discussion and Conclusion: "Absence of mannitol in Exela's product is not expected to affect renal clearance of palonosetron. After a single IV dosing of 10 mcg/kg [<sup>14</sup>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<sup>4</sup>. 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<sup>5</sup>."

Footnotes 4 and 5 from the CMC Review are the following:

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 (b)(4)% solution infused over a period of (b)(4) 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 Conclusion:

The overall conclusion is the following:

"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."

### **3.3 Final Recommendation**

The final recommendation by CMC is the following:

"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.”

## **4. Nonclinical Pharmacology/Toxicology**

### **4.1 First Review Cycle**

The Nonclinical Reviewer summarized the first review cycle conclusions/recommendations as follows:

“In the original NDA submission, the Applicant did not submit any nonclinical studies for this 505(b)(2) application. As concluded in the nonclinical review dated May 11, 2015, there are no nonclinical safety issues for the drug substance (palonosetron), as the Applicant relied on the Agency’s previous assessment of the safety of the approved drug Aloxi®. However, while no nonclinical safety issues were identified for the drug substance, based on the hypotonicity of the drug formulation which has zero osmolality, hemolysis was identified as a potential safety concern. In the absence of nonclinical data to support the safety of the proposed hypotonic formulation of the drug, the May 11, 2015 nonclinical review concluded that there was no basis upon which to make a recommendation from a pharmacology/toxicology standpoint. For nonclinical safety assessment of the proposed hypotonic formulation of the drug, a hemolysis study would be needed.”

### **4.2 Second (Current) Review Cycle**

#### **In Vitro Hemolysis Study:**

The Methods and Results are shown in Appendix 1 of this CDTL Review.

The Nonclinical Reviewer concluded the following:

“Under the current Class 2 Resubmission, the Applicant has submitted an *in vitro* hemolysis study to evaluate the hemolytic potential of Palonosetron HCL Injection in human blood. 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 Conclusion**

The Nonclinical Reviewer concluded the following:

“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.”

### **Labeling:**

The Nonclinical Reviewer additionally recommends that the proposed labeling be revised to include the following:

#### **Established Pharmacologic Class (HIGHLIGHTS and Section 11 DESCRIPTION)**

The EPC text phrase in the Applicant’s proposed label is: (b) (4)  
This should be changed to “serotonin-3 (5-HT3) receptor antagonist”, which is the FDA EPC text phrase for palonosetron. “Serotonin-3 (5-HT3) receptor antagonist” is also the EPC text phrase listed in the approved label dated 09/2014 for the listed drug (Aloxi®).

### **8.1 Pregnancy**

#### *Risk Summary*

There are no available data on palonosetron use in pregnant women to inform drug-associated risks. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral palonosetron to rats and rabbits during organogenesis at doses up to 1894 and 3789 times the recommended human intravenous dose, respectively [see Data]. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### *Data*

##### Animal Data

In animal reproduction studies, no effects on embryo-fetal development were observed in pregnant rats given oral palonosetron at doses up to 60 mg/kg/day (1894 times the recommended human intravenous dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (3789 times the recommended human intravenous dose based on body surface area) during the period of organogenesis.

### **8.2 Lactation**

#### *Risk Summary*

There are no data on the presence of palonosetron in human milk, the effects of palonosetron on the breastfed infant, or the effects of palonosetron on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for palonosetron and any potential adverse effects on the breastfed infant from palonosetron or from the underlying maternal condition.

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30, and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (Plasma AUC) of about 150 to 289 times the human exposure (AUC= 29.8 h•mcg/L) at the recommended intravenous dose of 0.25 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30, and 60 mg/kg/day and 15, 45, and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (Plasma AUC) of 137 and 308 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the *ex vivo* hepatocyte unscheduled DNA synthesis (UDS) test, or the mouse micronucleus test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test.

Palonosetron at oral doses up to 60 mg/kg/day (about 1894 times the recommended human intravenous dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

### **4.3 Final Recommendation**

An Approval Action is the final recommendation by the Nonclinical Pharmacology/ Toxicology discipline provided the labeling revisions described above are made.

## **5. Clinical Pharmacology/Biopharmaceutics**

### **5.1 First Review Cycle**

The following summary of clinical pharmacology and biopharmaceutics issues from the first review cycle is taken from the Clinical Review by Laurie Muldowney:

"No new clinical pharmacology information was submitted in support of this application. There are no major efficacy or safety issues from Clinical Pharmacology, which recommends approval. For more information see the Clinical Pharmacology Review by Sandhya Apparaju, PhD.

The Applicant requested a waiver of the *in vivo* bioequivalence study requirement as allowed under 21CFR 320.22(b)(1)(i) and (ii). The Applicant proposes that the

drug product's self-evident in vivo bioavailability or bioequivalence is based on the fact that it is a parenteral drug product and has the same active ingredient, dosage form, route of administration, and indications as the RLD, ALOXI® (palonosetron hydrochloride) Injection. Based on concerns regarding the osmolality of the proposed drug product, Biopharmaceutics determined that a biowaiver cannot be granted."

## 5.2 Second (Current) Review Cycle

Clinical Pharmacology: There were no new clinical pharmacology data in the resubmission, and no additional review of clinical pharmacology data was performed in the second (current) review cycle.

Biopharmaceutics: See Section 3.2 of this CDTL Review for a discussion of biopharmaceutics issues.

## 5.3 Final Recommendation

An Approval Action is the final recommendation by the Clinical Pharmacology and Biopharmaceutics disciplines.

## 6. Clinical Microbiology

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

## 7. Clinical/Statistical- Efficacy

No clinical trials were submitted in this 505(b)(2) application to support the efficacy of palonosetron hydrochloride injection. The Applicant relies on the effectiveness findings for ALOXI® (palonosetron hydrochloride) Injection, (NDA 021372) held by Helsinn Healthcare SA.

## 8. Safety

### 8.1 First Review Cycle

The following summary and conclusions of the pilot local irritation study is taken from the Clinical Review by Laurie Muldowney:

- Summary of Pilot Local Irritation Study: "A total of 32 patients were included in the pilot local irritation study, with 16 patients receiving single dose Palonosetron



Hydrochloride Injection 0.25 mg/2mL and 16 patients receiving single dose 0.9% Sodium Chloride Injection, USP 2 mL. Patients were observed in hospital for 48 hours and evaluated for local signs of phlebitis or infiltration at the IV site."

- Conclusion of Pilot Local Irritation Study: "Based on the safety data reviewed from Study EPS-2014-001, a double blinded, randomized, single dose, parallel local irritation pilot study, this medical reviewer finds that Palonosetron Hydrochloride Injection was well-tolerated locally, however, the study was not sufficient to draw conclusions on the overall safety of the drug product."

See Section 2.1 of this CDTL Review for the Clinical CR items from the first review cycle.

See also Section 3.1 of this CDTL Review for additional discussion of safety concerns from the first review cycle.

## 8.2 Second Review Cycle

The Clinical Reviewer (Aisha Johnson) noted that in the current submission, the Applicant addressed both of the clinical safety deficiencies in the CR Letter (see Section 2.1 of this CDTL Review).

Each of the CR items and the Applicant's Response to each are summarized below.

### Item #1

Clinical CR Item #1 was the following:

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.

#### A. Applicant's Response

The Applicant conducted an *in vitro* hemolysis study to address the potential for the hypotonic drug product to produce clinically relevant hemolysis.

B. Discussion/Conclusions:

The Methods and Results of this study are in Appendix 1 of this CDTL Review. The Nonclinical Reviewer's conclusions are discussed in Section 4.2 of this CDTL Review;

The Clinical Reviewer's discussion and conclusions are summarized below.

1. Dilution Ratios (Drug Volume:Total Blood Volume) in Pediatric Patients:

The Clinical Reviewer discussed the results of the in vitro hemolysis study as these relate to the calculated dilution ratios (drug volume/total blood volume) in pediatric patients across ages ranging from 1 month to 16 years as follows:

"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."

The table below is taken from the Clinical Review:

Table 3. Pediatric Dose/Volume Estimates and Calculated TBV Dilution<sup>1</sup>

Age	Weight*	Dose <sup>‡</sup> (20 mcg/kg)	Drug Volume <sup>§</sup> (0.125 mg/mL)	Average Total Blood Volume <sup>#</sup> (mL)	Dilution <sup>†</sup>
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
		<b>MAX DOSE 1.5 mg</b>	<b>MAX VOLUME 12 mL</b>		

Table above is taken from the Clinical Review by Aisha Johnson

\*Weight based on CDC growth charts, 5<sup>th</sup> percentile average of boys and girls

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

<sup>‡</sup>Dose (in mg) calculated as Weight X .020 mg/kg

<sup>§</sup>Drug volume (in mL) calculated as follows: Dose (in mg) / 0.125 mg/mL

<sup>†</sup>Dilution of 1: X calculated as follows: X = Average Total Blood Volume / Drug Volume

<sup>1</sup> [http://www.cdc.gov/growthcharts/data/who/grchrt\\_boys\\_24lw\\_100611.pdf](http://www.cdc.gov/growthcharts/data/who/grchrt_boys_24lw_100611.pdf) and <http://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf>

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."

**I agree with the clinical reviewer that the potential for clinically relevant hemolysis is low and does not preclude approval of palonosetron hydrochloride.**

**2. Instructions for the Infusion Line to be Flushed with Normal Saline:**

The Clinical Reviewer discussed the administration instructions (specifically instructions for the infusion line to be flushed with normal saline) as these relate to safety (specifically the concern of the risk of hemolysis) as follows:

"There is no regulatory requirement that small volume injectables be isotonic. The proposed palonosetron hydrochloride Dosage and Administration section of the label gives instructions for the infusion line to be flushed with normal saline (an isotonic solution) before and after administration. See below.

*Proposed Label (current as of 17 Feb 2016)*

**2.2 Instructions for Intravenous Administration**

- Do not mix with other drugs.
- Flush the infusion line with normal saline before and after administration of Palonosetron Injection.
- Inspect palonosetron solution visually for particulate matter and discoloration before administration.

The volume used to flush an infusion line can vary. However, "typically, in flushing an intravenous cannula, a 5 ml syringe of saline is emptied into the medication port..."<sup>2</sup> The current Aloxi label and the proposed palonosetron hydrochloride labels give instructions for flushing the infusion line before and after drug administration. In these cases, the 2mL dose of palonosetron hydrochloride will effectively be diluted in <sup>(b)(4)</sup> mL of an isotonic solution (saline)."

The Clinical Reviewer concluded the following:

"The use of normal saline to flush the infusion line prior to and after administration of the 2 mL adult dose of palonosetron hydrochloride will cause the hypotonic drug product to be diluted in a normotonic solution. The exact tonicity of the resultant mixture will be dependent on the volume of normal saline used. However, in all cases, the resultant mixture will have a tonicity >0 mOSM/mL. It is this higher

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<sup>2</sup> Longmore, Murray; Ian B. Wilkinson; Edward H. Davidson; Alexander Foulkes; Ahmad R. Mafi (2010). *Oxford Handbook of clinical Medicine*.

tonicity solution that will reach the patient's blood stream. In summary, the use of a normal saline flush, further lowers the risk of hemolysis related to the use of the hypotonic drug product."

**I agree with the clinical reviewer that the use of a normal saline flush further lowers the risk of hemolysis related to the use of this hypotonic drug product.**

## **Item #2**

Clinical CR Item #2 was the following:

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.

### **A. Applicant's Response**

In their response, the Applicant acknowledged the potential for dosing errors (b) (4)

➤ **Indication** (b) (4): Chemotherapy-Induced Nausea and Vomiting

- 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

**Dosage** (b) (4): The recommended adult dosage is **0.25** (b) (4) **mg** administered intravenously as a **single dose over 30 seconds**. Dosing should occur approximately 30 minutes before the start of chemotherapy

Note that for the listed drug Aloxi, the concentration is **0.05 mg/mL** (currently marketed as a **0.075 mg/1.5 mL** single use vial and a **0.25 mg/5 mL** single use vial) whereas for the proposed product, the concentration is **0.125 mg/mL** (proposed as a **0.25 mg/2 mL** single use vial). (b) (4)

(b) (4)

B. Discussion/Conclusions:

(b) (4)

### **8.3 Final Recommendation**

An Approval Action is the final recommendation from a Safety standpoint.

### **9. Advisory Committee Meeting**

During the current review cycle, this application was not presented to an Advisory Committee.

### **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 505(a)(1) 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."

-  (b) (4)

## **11. Other Relevant Regulatory Issues**

### **11.1 505(b)(2) Regulatory Issues**

#### **First Review Cycle**

In the first review cycle, the following Regulatory CR item was sent:

1. It appears that Helsinn and Roche received notice under 21 CFR 314.52. With respect to any other owner(s) of the patent(s) that are the subject of the certification or the representative designated by the owner to receive notice, please submit to FDA adequate documentation of receipt of notice, or re-notify the relevant recipients and submit to FDA adequate documentation of receipt of notice. You did not submit a return receipt or letter acknowledging receipt by the person(s) provided notice. See 21 CFR 314.52. We note that FDA did not agree to another form of documentation in advance.

#### **Current Review Cycle**

In the current review cycle, this CR item was addressed as follows:

The applicant submitted amendments to address the Regulatory CR item above.

On December 17, 2015, an information request (IR) was issued requesting the applicant to submit additional amendments to address requirements under 21 CFR 314.52; the applicant responded to this IR.

On February 29, 2016, the CDER 505(b)(2) committee met to discuss this application. The Committee reviewed the responses and indicated the applicant's responses were adequate.

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. See Section 13.1 of this CDTL Review.

## 12. Labeling

### 12.1 Physician Labeling

Revisions to the Physician Labeling included the following:

- Section 1.1: In Section 1.1, the heading was revised to include "in Adults". See below (*emphasis added*):

#### 1.1 Chemotherapy-Induced Nausea and Vomiting *in Adults*

- Section 6.1: Section 6.1 (Adverse Reactions - Clinical Trials Experience) was revised to include the statement below.

The safety of Palonosetron HCl Injection has been established from adequate and well-controlled studies of another intravenous formulation of palonosetron HCl [*see Clinical Studies (14)*]. Below is a display of the adverse reactions of palonosetron HCl in these adequate and well-controlled studies.

- Sections 8.1 and 8.2: Section 8.1 (Pregnancy) and Section 8.2 (Lactation) were converted to the PLLR format.
  - The "Pregnancy" subsection was formatted in the PLLR format to include the "Risk Summary" and "Data" subsections.
  - The "Lactation" subsection was formatted in the PLLR format to include the "Risk Summary" subsection.

See DPMH Review from the previous review cycle.

- Section 8.4: Section 8.4 (Pediatric Use) was revised to include the following statement (*emphasis added*):

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

The rationale for this statement is provided in the DPMH Pediatric Review as follows: "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 'this product has

not been approved for pediatric use' is a true statement and is an alternative statement as allowed under the regulations.”

- Section 8.5: Section 8.5 (Geriatric Use) was revised to include the following statement:

No overall differences in safety were observed between older and younger subjects in these studies, (b) (4)

- Section 14: Section 14 (Clinical Studies) was revised to include the statement below.

The safety and efficacy of Palonosetron HCl Injection have been established based on adequate and well-controlled adult studies of another intravenous formulation of palonosetron HCl in chemotherapy induced nausea and vomiting. Below is a display of the results of these adequate and well-controlled studies of palonosetron HCl.

## 12.2 Patient Package Insert

Labeling revisions included those shown below. See DMPP Patient Labeling Review.

- "What should I tell my doctor before receiving Palonosetron Injection?" section: The following statement was added beneath the statement "Tell your doctor about all of the medicines you take including prescription and over-the-counter medicines, vitamins and herbal supplements." to reflect Section 7.1 (Drug Interactions - Serotonergic Drugs) of the Prescribing Information (PI):
- "Palonosetron Injection and certain other medicines can affect each other, causing serious side effects."
- "What are the possible side effects of Palonosetron Injection?" section: The following serious side effects were added for consistency with the Section 5 (Warnings and Precautions) of the PI:
- Palonosetron Hydrochloride Injection may cause serious side effects, including:**
- **Serious allergic reactions.** Palonosetron Hydrochloride Injection can cause allergic reactions that can sometimes be serious. Tell your doctor or nurse right away if you have any of the following symptoms of a serious allergic reaction with Palonosetron Hydrochloride Injection:
    - hives
    - swollen face
    - breathing trouble
    - chest pain
  - **Serotonin Syndrome.** A possible life-threatening problem called serotonin syndrome can happen with medicines called 5-HT<sub>3</sub> receptor antagonists, including



Palonosetron Hydrochloride Injection, especially when used with medicines used to treat depression and migraine headaches called serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs) and certain other medicines. Tell your doctor or nurse right away if you have any of the following symptoms of serotonin syndrome:

- agitation, seeing things that are not there (hallucinations), confusion, or coma
- fast heartbeat or unusual and frequent changes in your blood pressure
- dizziness, sweating, flushing, or fever
- tremors, stiff muscles, muscle twitching, overactive reflexes, or loss of coordination
- seizures
- nausea, vomiting, or diarrhea

### 12.3 Carton and Container Labeling

DMEPA recommended the changes below to the carton and container labels prior to approval of the current NDA. These comments were sent to the Applicant on February 1, 2016.

1. Add a cautionary statement (b) (4) to the principal display panel that this product is higher in concentration than the reference drug product to avoid dosing errors. For example, (b) (4)
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)
3. Increase the prominence of the established name by increasing the font size.
4. As currently presented, the NDC number is located (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 (b) (4) Rx only statements on the side panel. Please move one statement to the bottom right corner of the principal display panel (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 “(b) (4)” statement since the proposed adult dosage for this formulation is the entire vial (0.25 mg).
9. Revise the “(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 February 5, 2016, the Applicant submitted a revised proposed carton container label. The following additional comments were sent to the Applicant on March 4, 2016:

1. We recommend bolding the cautionary statement, (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.

On March 17, 2016, the Applicant submitted a revised proposed carton container label. The above comments were addressed.

## **13. Recommendations/Risk Benefit Assessment**

### **13.1 Recommended Regulatory Action**

All of the review disciplines recommended an Approval action. This Reviewer concurs with the recommendations from each of the disciplines; however, Tentative Approval is recommended (see Section 11.1 of this CDTL Review).

### **13.2 Risk Benefit Assessment**

An injectable palonosetron hydrochloride product has been marketed in the US since 2003 under the tradename Aloxi. 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 on the review of the data submitted in both the initial and current review cycles, these differences are not expected to impact efficacy or safety. Absence of these agents is not expected to impact PK of palonosetron (see Biopharmaceutics conclusions in Section 3.2). The product was determined to be well-tolerated locally based on the review of the local irritation study (see Clinical conclusions in Section 8.1). The product is not expected to have hemolytic potential based on the review of the in vitro hemolysis study (see Nonclinical conclusions in Section 4.2 and Clinical conclusions in Section 8.2).

Possible risks of the new formulation (b) (4) CINV indication [recommended dose of 0.25 mg] and only one dosage strength formulation [0.25 mg/2mL single use vial] (b) (4)

These risks can be mitigated through professional labeling (see Section 12.3 of this CDTL Review).

### **13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)**

No special postmarketing risk management activities are recommended for this Application.

### **13.4 Recommendation for Postmarketing Required Pediatric Studies**

No postmarketing required pediatric studies are recommended for this Application.

### **13.5 Recommendation for other Postmarketing Study Requirements (PMRs)**

None of the primary review disciplines had recommendations for postmarketing requirements.

### **13.6 Recommendation for Postmarketing Study Commitments (PMCs)**

None of the primary review disciplines had recommendations for postmarketing commitments.

### **13.7 Recommended Comments to Applicant**

None.

## APPENDIX 1: IN VITRO HEMOLYSIS STUDY

The following methods and result of the in vitro hemolysis study (Study No. CYP1177-R4) are taken from the Nonclinical Review by Tracy Behrsing.

**Methods:** The purpose of this study was to evaluate the hemolytic potential of Palonosetron HCL Injection in human blood. In this study, the following four batches of the test article (supplied as a 0.125 mg/mL solution) were used: Lot# XLNC1306, XLNC1307, XLNC1308, and XLNB1421. According to the study report, two-fold dilutions of each test article were prepared in saline and then diluted into aliquots of human, heparinized blood. The test concentration range was 0.098 to 12.5 mcg/mL. Following incubation at 37°C for 45 min, the blood was centrifuged to separate the cells from plasma. An aliquot of plasma was then diluted with Drabkin's reagent, and the OD540 was measured. The degree of hemolysis was determined based upon a calibration curve prepared by dilution of non-centrifuged blood. The reference compound (positive control) was Triton X-100.

In response to a nonclinical Information Request dated October 29, 2015, the Applicant stated that the high concentration sample (12.5 mcg/mL) was prepared by diluting the test article 1/10 directly into blood without any pre-dilution of the test article with saline. The high concentration sample was performed based upon the proposed labeling which indicates that the drug product is to be administered intravenously as a single dose. According to the proposed labeling, dilution of the drug product prior to injection is not required. The remaining seven concentrations were prepared by two-fold dilution of the test article in saline, followed by a 1/10 dilution into blood.

### Results:

In this study, the mean percent lysis ranged from 0.4 to 1.5% over the test concentration range of 0.098 to 12.5 mcg/mL. Although the mean percent lysis following treatment with Palonosetron HCL Injection exceeded that of the vehicle and untreated controls (0.4 and 0.5%, respectively), the maximum mean hemolysis observed with the test article was  $\leq 1.5\%$ . In addition, the maximum mean hemolysis ( $1.5 \pm 0.48\%$  at 12.5 mcg/mL Palonosetron HCL Injection) was  $\geq 6$  times lower than that observed for the reference compound (mean percent lysis was 9.2 and 91.5% for 0.1% and 1% Triton X-100, respectively). Results of the hemolysis study are summarized in the Applicant's table below.

4.1 Hemolysis Data Summary: Human Blood

Test Article	Lot#	Test Conc.	% Lysis 1 <sup>st</sup> replicate	% Lysis 2 <sup>nd</sup> replicate	% Lysis 3 <sup>rd</sup> replicate	Mean % Lysis	SD
Vehicle	N/A	-	0.4%	0.4%	0.5%	0.4%	0.02%
Untreated		-	0.5%	0.5%	0.5%	0.5%	0.01%
Triton X-100		0.1%	9.3%	9.2%	8.9%	9.2%	0.2%
Triton X-100		1%	98.7%	92.8%	83.1%	91.5%	7.8%
Palonosetron HCl injection	XLNC1306	12.5 µg/mL	1.1%	2.0%	1.0%	1.4%	0.54%
		6.25 µg/mL	0.4%	0.5%	0.4%	0.4%	0.02%
		3.125 µg/mL	0.5%	0.5%	0.4%	0.5%	0.05%
		1.56 µg/mL	0.4%	0.5%	0.5%	0.5%	0.03%
		0.78 µg/mL	0.5%	0.5%	0.4%	0.5%	0.05%
		0.39 µg/mL	0.5%	0.6%	0.5%	0.5%	0.10%
		0.195 µg/mL	0.4%	0.5%	0.5%	0.4%	0.04%
		0.098 µg/mL	0.4%	0.5%	0.4%	0.4%	0.02%
	XLNC1307	12.5 µg/mL	2.1%	1.3%	1.2%	1.5%	0.48%
		6.25 µg/mL	0.4%	0.4%	0.4%	0.4%	0.02%
		3.125 µg/mL	0.4%	0.4%	0.4%	0.4%	0.02%
		1.56 µg/mL	0.4%	0.5%	0.4%	0.4%	0.02%
		0.78 µg/mL	0.4%	0.5%	0.4%	0.4%	0.01%
		0.39 µg/mL	0.4%	0.5%	0.4%	0.4%	0.01%
		0.195 µg/mL	0.4%	0.4%	0.4%	0.4%	0.01%
		0.098 µg/mL	0.4%	0.4%	0.4%	0.4%	0.04%
	XLNC1308	12.5 µg/mL	2.2%	0.9%	0.7%	1.3%	0.79%
		6.25 µg/mL	0.4%	0.5%	0.5%	0.4%	0.03%
		3.125 µg/mL	0.4%	0.5%	0.4%	0.4%	0.02%
		1.56 µg/mL	0.4%	0.5%	0.5%	0.4%	0.03%
		0.78 µg/mL	0.4%	0.5%	0.5%	0.4%	0.01%
		0.39 µg/mL	0.4%	0.5%	0.5%	0.5%	0.05%
		0.195 µg/mL	0.4%	0.5%	0.5%	0.5%	0.04%
		0.098 µg/mL	0.4%	0.5%	0.4%	0.4%	0.03%
	XLNB1421	12.5 µg/mL	0.9%	1.3%	0.5%	0.9%	0.37%
		6.25 µg/mL	0.5%	0.4%	0.5%	0.5%	0.04%
		3.125 µg/mL	0.5%	0.5%	0.6%	0.5%	0.04%
		1.56 µg/mL	0.5%	0.5%	0.6%	0.5%	0.04%
0.78 µg/mL		0.5%	0.5%	0.6%	0.5%	0.05%	
0.39 µg/mL		0.9%	0.8%	1.1%	0.9%	0.12%	
0.195 µg/mL		0.5%	0.4%	0.6%	0.5%	0.08%	
0.098 µg/mL		0.5%	0.4%	0.6%	0.5%	0.06%	

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/s/  
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ANIL K RAJPAL  
03/22/2016