# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 207963Orig1s000

# PHARMACOLOGY REVIEW(S)

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

# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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|---|---|
| Application number: | 207963 |
| Supporting document/s: | 18, 20 |
| Applicant's letter date: | SDN 18 - September 15, 2015<br>SDN 20 – November 2, 2015 |
| CDER stamp date: | SDN 18 - September 22, 2015<br>SDN 20 – November 3, 2015 |
| Product: | Palonosetron Injection |
| Indication: | Prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy, (b) (4) |
| Applicant: | Exela Pharma Sciences, LLC. |
| Review Division: | Division of Gastroenterology and Inborn Errors Products (DGIEP) |
| Reviewer: | Tracy Behrsing, Ph.D. |
| Supervisor/Team Leader: | Sushanta Chakder, Ph.D. |
| Division Director: | Donna Griebel, M.D. |
| Project Manager: | Mary Chung, PharmD. |

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information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 207963.

# 1 Executive Summary

## 1.1 Introduction

Exela Pharma Sciences, LLC. seeks approval of Palonosetron Injection for use in adults for the prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy. The Palonosetron Injection NDA was originally submitted on August 7, 2014 under the 505(b)(2) pathway. The reference listed drug is Aloxi® (palonosetron hydrochloride) Injection, which was initially approved in the U.S. in 2003. The current submission (SDN 18) is a Class 2 Resubmission of NDA 207963. In this resubmission, the Applicant has provided information to address clinical, product quality, and regulatory deficiencies identified during the review of the original NDA submission and outlined in the Complete Response Letter sent to the Applicant on June 15, 2015. In addition, based on the Agency's concern on the hypotonicity of the product, the Applicant conducted an *in vitro* hemolysis study with the drug product, and the study report was submitted.

## 1.2 Brief Discussion of Nonclinical Findings

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.

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 ≤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.

### 1.3 Recommendations

#### 1.3.1 Approvability

From a nonclinical perspective, the NDA is approvable.

#### 1.3.2 Additional Non Clinical Recommendations

None

#### 1.3.3 Labeling

Recommended revisions to the Established Pharmacologic Class and sections 8.1, 8.3, and 13.1 of the Applicant's proposed labeling are included in the nonclinical review dated May 11, 2015.

## 2 Drug Information

### 2.1 Drug

Palonosetron Injection

**CAS Registry Number:** 135729-62-3

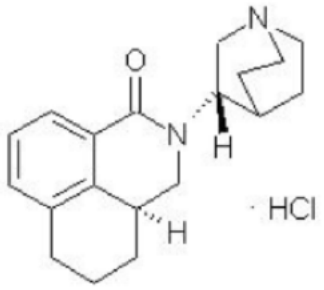
**Generic Name:** Palonosetron hydrochloride

**Code Name:** None

**Chemical Name:** (3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[de]isoquinoline hydrochloride

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

**Structure or Biochemical Description:**




**Pharmacologic Class:** serotonin-3 (5-$HT_3$) receptor antagonist

### 2.2 Relevant INDs, NDAs, BLAs and DMFs

PIND 116583 (palonosetron hydrochloride)
DMF (b) (4) (palonosetron hydrochloride)
DMF (b) (4)

DMFs (b) (4)
NDA 021372 Aloxi® (palonosetron hydrochloride) Injection

## 2.3 Drug Formulation

Palonosetron Injection is a sterile, preservative-free, injectable solution with a concentration of 0.125 mg/mL palonosetron (as base). The dosage form and strength is 0.25 mg (free base) per 2 mL in a single-dose glass vial, supplied as 0.28 mg palonosetron hydrochloride. The proposed drug product differs from the reference listed drug (Aloxi®) with respect to the active ingredient concentration, pH, and the inactive ingredients. The active ingredient concentration of the reference listed drug product is 0.25 (b) (4) mg/5 mL or 0.075 mg/1.5 mL. The active ingredient concentration in the Applicant's proposed drug product is 0.125 mg/mL (as base). The pH of the reference drug product is 4.5 to 5.5, whereas the pH range of the proposed drug product is 6.5 - 8.5. Finally, the reference 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.

## 2.4 Comments on Novel Excipients

None

## 2.5 Comments on Impurities/Degradants of Concern

An evaluation of the proposed specifications is included in the nonclinical review dated May 11, 2015, and there are no safety concerns.

## 2.6 Proposed Clinical Population and Dosing Regimen

The original New Drug Application (SND 01) proposed the use of palonosetron injection in adults for prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy (b) (4) The recommended adult dosage for the chemotherapy-induced nausea and vomiting indication is 0.25 mg administered intravenously as a single dose over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy. (b) (4)

Under the current submission (SDN 18), the Applicant has revised the proposed labeling (b) (4) Thus, the revised proposed labeling contains only one indication: chemotherapy-induced nausea and vomiting in adult patients.

## 2.7 Regulatory Background

The Applicant submitted NDA 207963 on August 7, 2014 under the 505(b)(2) pathway. A Complete Response Letter identifying clinical, product quality, and regulatory deficiencies was sent to the Applicant on June 15, 2015. While no nonclinical deficiencies were identified in the letter, clinical deficiencies pertaining to the safety of the proposed formulation relative to its hypotonicity were included. The letter stated that

the Applicant has not established that the hypotonicity of the drug product will not result in clinically relevant hemolysis. To address this deficiency, the Applicant was informed that data could be provided from literature sources, nonclinical studies, or through review of intravenous products with comparable formulation characteristics. In particular, the Applicant should address the potential for hemolysis in patients with smaller blood volumes in whom the potential for hemolysis may be greater.

The current submission (SDN 18) is a Class 2 Resubmission of NDA 207963. The submission includes responses to the deficiencies identified in the June 15, 2015 action letter. In addition, the Applicant also submitted the results of the *in vitro* hemolysis study with the drug product.

# 3 Studies Submitted

## 3.1 Studies Reviewed

Study No. CYP1177-R4 (Human Blood Hemolysis Screening of a Test Agent)

## 3.2 Studies Not Reviewed

None

## 3.3 Previous Reviews Referenced

NDA 207963 nonclinical review dated May 11, 2015 (T. Behrsing, Ph.D., DGIEP)

# 4 Pharmacology

No studies were submitted.

# 5 Pharmacokinetics/ADME/Toxicokinetics

No studies were submitted.

# 6 General Toxicology

No studies were submitted.

# 7 Genetic Toxicology

No studies were submitted.

# 8 Carcinogenicity

No studies were submitted.

# 9 Reproductive and Developmental Toxicology

No studies were submitted.

# 10 Special Toxicology Studies

**Human Blood Hemolysis Screening of a Test Agent (Study No. CYP1177-R4; Test Facility: (b) (4))**

**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 37ºC 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 $OD_{540}$ 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 ≤1.5%. In addition, the maximum mean hemolysis (1.5 ±0.48% at 12.5 mcg/mL Palonosetron HCL Injection) was ≥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 1st replicate | % Lysis 2nd replicate | % Lysis 3rd 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% |

# 11 Integrated Summary and Safety Evaluation

Exela Pharma Sciences, LLC. seeks to market Palonosetron Injection, a serotonin-3 (5-HT3) receptor antagonist, for use in adult patients for the prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy. The Applicant seeks approval of palonosetron injection under a 505(b)(2) NDA. The reference listed drug is Aloxi® which is approved for use in adults as well as pediatric patients aged 1 month to less than 17 years. The Applicant's proposed drug product differs from the reference listed drug formulation with respect to the active ingredient concentration, pH, and the inactive ingredients. The proposed drug product contains only the drug substance (palonosetron hydrochloride) dissolved in water for injection,

and does not contain any excipients, such as buffers, tonicity agents, preservatives or chelating agents.

In support of the marketing application, the Applicant relied on the Agency's previous determination of safety of palonosetron. According to the approved label for Aloxi® dated September 2014, 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. However, a clastogenic effect was observed in the Chinese hamster ovarian (CHO) cell chromosomal aberration test. In a 104-week carcinogenicity study in CD-1 mice, palonosetron was not tumorigenic at oral doses of 10, 30 and 60 mg/kg/day. In a 104-week oral gavage carcinogenicity study in Sprague-Dawley rats, palonosetron was administered to males at 15, 30 and 60 mg/kg/day and females at 15, 45 and 90 mg/kg/day. In male rats, treatment with palonosetron resulted in 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 female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma. Palonosetron had no effect on fertility and reproductive performance of male and female rats at oral doses up to 60 mg/kg/day. There were no effects on embryofetal development in pregnant rats and rabbits treated with oral doses of palonosetron up to 60 mg/kg/day during the period of organogenesis.

During the first review cycle for this NDA, hemolysis was identified as a potential safety concern due to the hypotonicity of the proposed drug formulation. Given this potential concern, the Applicant submitted an *in vitro* hemolysis study to evaluate the hemolytic potential of Palonosetron HCL Injection in human blood. In the hemolysis study, four batches of the test article were tested over a concentration range of 0.098 to 12.5 mcg/mL. 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) since dilution of the drug product prior to injection is not required according to the proposed labeling. The remaining seven concentrations were prepared by two-fold dilution of the test article in saline, followed by a 1/10 dilution into blood. Overall, the mean percent lysis ranged from 0.4 to 1.5% over the test concentration range evaluated. While the mean percent lysis following treatment with Palonosetron HCL Injection was greater than that of the vehicle and untreated controls (0.4 and 0.5%, respectively), the maximum mean percent lysis observed with the test article was ≤1.5% and at least 6 times lower than that observed for the positive control . This suggests that the test article is not expected to have a hemolytic potential. With respect to the potential for hemolysis in patients with smaller blood volumes, the Applicant stated that the higher concentration evaluated in the hemolysis study (representing a 10% dilution in blood) was chosen to address this issue. The Applicant stated that based on the estimated blood volume in a female at the $5^{th}$ percentile (2.4 L), a single 2 mL injection of the drug formulation would represent <0.1% of the total blood volume.

In conclusion, there are no nonclinical safety issues for the drug substance based on the Agency's previous determination of safety of palonosetron. In addition, the results of the *in vitro* hemolysis study with Palonosetron HCl Injection suggest that the proposed drug formulation is not expected to cause a clinically relevant hemolysis. Therefore, no safety concerns were identified from a nonclinical perspective. The Applicant should be asked to revise the labeling as recommended in the nonclinical review dated May 11, 2015.

# 12 Appendix/Attachments

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/s/

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TRACY L BEHRSING
02/19/2016

SUSHANTA K CHAKDER
02/19/2016

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
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# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

| | |
|---|---|
| Application number: | 207963 |
| Supporting document/s: | 01 |
| Applicant's letter date: | SDN 01 - August 7, 2014 |
| CDER stamp date: | SDN 01 - August 15, 2014 |
| Product: | Palonosetron Injection |
| Indication: | Prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy (b) (4) |
| Applicant: | Exela Pharma Sciences |
| Review Division: | Division of Gastroenterology and Inborn Errors Products (DGIEP) |
| Reviewer: | Tracy Behrsing, Ph.D. |
| Supervisor/Team Leader: | Sushanta Chakder, Ph.D. |
| Division Director: | Donna Griebel, M.D. |
| Project Manager: | James Carr, MPAS, PA-C |

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# 1 Executive Summary

## 1.1 Introduction

Exela Pharma Sciences seeks approval of Palonosetron Injection for use in adults for the prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy (b) (4) The Palonosetron Injection NDA was submitted under the 505(b)(2) pathway. The reference listed drug is Aloxi® (palonosetron hydrochloride) Injection, which was initially approved in the U.S. in 2003.

## 1.2 Brief Discussion of Nonclinical Findings

The Applicant did not conduct any new nonclinical studies to support the marketing application. Thus, nonclinical safety assessment of palonosetron is based upon the previously approved drug Aloxi®.

The proposed formulation of the drug is hypotonic with zero osmolality. Based on the hypotonicity of the drug product, hemolysis is a potential safety concern. While the Applicant stated under PIND 116583 that a hemolysis study and injection site sensitivity study in laboratory animals would be submitted in the NDA, these studies were not included in the marketing application. It is unknown whether there are previously approved products that have zero osmolality.

## 1.3 Recommendations

### 1.3.1 Approvability

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 palonosetron. However, in the absence of any nonclinical data supporting the safety of the proposed hypotonic formulation of the drug, there is no basis upon which to make a recommendation from a pharmacology/toxicology standpoint. Based on the hypotonicity of the drug formulation, hemolysis is a potential safety concern.

### 1.3.2 Additional Non Clinical Recommendations

For nonclinical safety assessment of the proposed hypotonic formulation of the drug, a hemolysis study is needed.

### 1.3.3 Labeling

**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-$HT_3$) receptor antagonist", which is the FDA EPC text phrase for palonosetron. "Serotonin-3 (5-$HT_3$) receptor antagonist" is also the EPC text phrase listed in the approved label dated 09/2014 for the reference listed drug (Aloxi®).

**Applicant's Proposed Version:**

**8.1 Pregnancy**

(b) (4)

**Evaluation:** This subsection should be revised according to PLLR labeling format. The recommended revisions were developed in collaboration with the Maternal Health team.

**Recommended Version:**

**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.

**Applicant's Proposed Version:**

(b) (4)

**Evaluation:** This subsection should be revised according to PLLR labeling format. The recommended revisions were developed in collaboration with the Maternal Health team.

**Recommended Version:**

**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.

**Applicant's Version:**

**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 ng•h/mL) 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.

**Evaluation:** This subsection is the same as that in the currently approved label for Aloxi® (09/2014), with the exception of human exposure (AUC) units. This human exposure (AUC) units should be changed from ng•h/mL to h•mcg/Lfor consistency with the currently approved label for the reference listed drug.

**Recommended Version:**

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.

# 2 Drug Information

## 2.1 Drug

Palonosetron Injection

**CAS Registry Number:** 135729-62-3

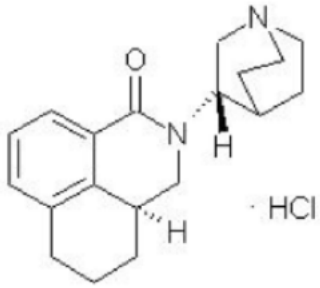
**Generic Name:** Palonosetron hydrochloride

**Code Name:** None

**Chemical Name:** (3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[de]isoquinoline hydrochloride

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

**Structure or Biochemical Description:**




**Pharmacologic Class:** serotonin-3 ($5\text{-}HT_3$) receptor antagonist

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

PIND 116583 (palonosetron hydrochloride)
DMF [redacted] (palonosetron hydrochloride; letter of authorization included)
DMF [redacted] letter of authorization included)
DMFs [redacted] letter of authorization included)
NDA 021372 Aloxi® (palonosetron hydrochloride) Injection

## 2.3 Drug Formulation

Palonosetron Injection is a sterile, preservative-free, injectable solution with a concentration of 0.125 mg/mL palonosetron (as base). The dosage form and strength is 0.25 mg (free base) per 2 mL in a single-dose glass vial, supplied as 0.28 mg palonosetron hydrochloride.

In the original NDA submission (SDN 01), the Applicant stated that the drug product [redacted] However, in a subsequent amendment to the NDA (SND 03; Received January 22, 2015), the Applicant amended the application to provide a revised proposed commercial batch record [redacted] revised drug product specification with a pH range of 6.5 – 8.5. Thus, the drug product will contain only the drug substance (palonosetron hydrochloride) dissolved in water for injection.

The proposed drug product differs from the reference listed drug (Aloxi®) with respect to the active ingredient concentration, pH, and the inactive ingredients. The active ingredient concentration of the reference listed drug product is 0.25 [redacted] mg/5 mL or 0.075 mg/1.5 mL. The active ingredient concentration in the Applicant's proposed drug product is 0.125 mg/mL (as base). The pH of the reference drug product is 4.5 to 5.5, whereas the pH range of the proposed drug product is 6.5 - 8.5. Finally, the reference listed drug contains the following inactive ingredients: mannitol [redacted] disodium edetate [redacted] citrate [redacted], and water for injection. The Applicant's proposed formulation does not contain any excipients, such as buffers, tonicity agents, preservatives, or chelating agents. According to the Applicant's response to an Information Request, the formulation has zero osmolality (0 mOsm/kg) (SDN 06, Received March 9, 2015).

## 2.4 Comments on Novel Excipients

There are no novel excipients in the proposed drug product.

## 2.5 Comments on Impurities/Degradants of Concern

Drug Substance: The proposed specifications for the (b) (4) % each. The specification for single unknown impurities is no more than (b) (4) %. These specifications are acceptable in accordance with ICH Q3A Impurities in New Drug Substances.

The proposed specification for heavy metals is (b) (4) ppm (individual heavy metals are not identified in the specification). At the recommended clinical dose of 0.25 mg, the maximum exposure to heavy metals is (b) (4) µg at the proposed specification of (b) (4) ppm. The lowest permitted daily exposure (PDE) for elemental impurities in parenteral drug products is 2 µg/day (b) (4) per ICH Q3D Guideline for Elemental Impurities ( (b) (4) version dated December 2014). Thus, the proposed specification for heavy metals is acceptable.

The proposed specifications for solvents (b) (4) meet limits in ICH Q3C Impurities: Residual Solvents, and therefore are acceptable.

Drug Product: The proposed specifications for single individual unknown and total impurities in the drug product are no more than (b) (4) %, respectively. The specification for unknown impurities meets the identification threshold of (b) (4) µg total daily intake, whichever is lower, for drug products with a maximum daily dose < 1 mg (ICH Q3(R2) Impurities in New Drug Products). Thus, this is acceptable.

## 2.6 Proposed Clinical Population and Dosing Regimen

This 505(b)(2) New Drug Application proposes the use of palonosetron injection in adults for prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy (b) (4) The recommended adult dosage for the chemotherapy-induced nausea and vomiting indication is 0.25 mg administered intravenously as a single dose over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy. (b) (4)

## 2.7 Regulatory Background

None

# 3 Studies Submitted

No nonclinical studies were submitted in this 505(b)(2) application.

### 3.1 Studies Reviewed

None

### 3.2 Studies Not Reviewed

None

### 3.3 Previous Reviews Referenced

None

# 4 Pharmacology

No studies were submitted.

# 5 Pharmacokinetics/ADME/Toxicokinetics

No studies were submitted.

# 6 General Toxicology

No studies were submitted.

# 7 Genetic Toxicology

No studies were submitted.

# 8 Carcinogenicity

No studies were submitted.

# 9 Reproductive and Developmental Toxicology

No studies were submitted.

# 10 Special Toxicology Studies

No studies were submitted.

# 11 Integrated Summary and Safety Evaluation

Exela Pharma Sciences seeks to market Palonosetron Injection, a serotonin-3 (5-HT3) receptor antagonist, for use in adult patients for the prevention of nausea and vomiting associated with moderately and highly emetogenic cancer chemotherapy (b) (4)

(b) (4) The Applicant seeks approval of palonosetron injection under a 505(b)(2) NDA. The reference listed drug is Aloxi® which is indicated for use in adults as well as pediatric patients aged 1 month to less than 17 years. The Applicant's proposed drug product differs from the reference listed drug with respect to the active ingredient concentration, pH, and the inactive ingredients. The proposed drug product will contain only the drug substance (palonosetron hydrochloride) dissolved in water for injection, and does not contain any excipients, such as buffers, tonicity agents, preservatives or chelating agents.

The Applicant did not conduct any nonclinical studies in support of the marking application. Thus, the Applicant relied on the Agency's previous determination of safety of palonosetron. According to the approved label for Aloxi® dated 09/2014, 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. However, a clastogenic effect was observed in the Chinese hamster ovarian cell chromosomal aberration test. In a 104-week carcinogenicity study in CD-1 mice, palonosetron was not tumorigenic at oral doses of 10, 30 and 60 mg/kg/day. In a 104-week oral gavage carcinogenicity study in Sprague-Dawley rats, palonosetron was administered to males at 15, 30 and 60 mg/kg/day and females at 15, 45 and 90 mg/kg/day. In male rats, treatment with palonosetron resulted in 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 female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma. Palonosetron had no effect on fertility and reproductive performance of male and female rats at oral doses up to 60 mg/kg/day. There were no effects on embryofetal development in pregnant rats and rabbits treated with oral doses of palonosetron up to 60 mg/kg/day during the period of organogenesis.

With respect to the drug product, the proposed formulation of the drug is hypotonic with zero osmolality. Hemolysis is a potential safety concern based on the hypotonicity of the drug formulation. Under PIND 116583, the Agency stated in Preliminary Meeting Comments dated November 30, 2012 that removal of the tonicity agent (mannitol) and/or changes in pH may affect safety (i.e., injection site reactions). Thus, the Applicant was informed that they would need to adequately justify that these changes do not affect the safety of the proposed product. In a letter dated December 19, 2012, The Applicant requested clarification as to what safety studies should be performed to address these changes in formulation. The Applicant stated that a hemolysis study and injection site sensitivity study in laboratory animals were planned and would be submitted in the NDA. The Applicant also asked what additional studies should be performed, if any, to adequately justify the formulation differences. FDA's response dated February 8, 2013 stated that a local irritation study in healthy volunteers should be conducted to address potential safety concerns, and a protocol for this human study was subsequently submitted for Agency review. In the current marketing application,

the Applicant submitted a local irritation study in healthy volunteers but no nonclinical studies were included.

Overall, there are no nonclinical safety issues for the drug substance (palonosetron). However, in the absence of any nonclinical data supporting the safety of the proposed hypotonic formulation of the drug with zero osmolality, there is no basis upon which to make a recommendation from a pharmacology/toxicology standpoint. In addition, the Applicant should be asked to revise the labeling as recommended.

# 12 Appendix/Attachments

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

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/s/

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TRACY L BEHRSING
05/11/2015

SUSHANTA K CHAKDER
05/11/2015