CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-233

PHARMACOLOGY REVIEW(S)
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22,233
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 10/24/07
PRODUCT: ALOXI® (palonosetron HCl) Capsules
INTENDED CLINICAL POPULATION: Patients receiving moderately emetogenic cancer chemotherapy
SPONSOR: Helsinn Healthcare SA
DOCUMENTS REVIEWED: Volumes 1-2
REVIEW DIVISION: Division of Gastroenterology Products (HFD-180)
PHARM/TOX REVIEWER: David B. Joseph, Ph.D.
ACTING PHARM/TOX TEAM LEADER: Sushanta K. Chakder, Ph.D.
DIVISION DIRECTOR: Donna Griebel, M.D.
PROJECT MANAGER: Jagjit Grewal, M.P.H.

Date of review submission to Division File System (DFS): June 25, 2008
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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The application is recommended for approval.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

Recommendations are shown below for the following sections and subsections:


Sponsor’s Proposed Version:

“HIGHLIGHTS OF PRESCRIBING INFORMATION”

“INDICATIONS AND USAGE

ALOXI Capsules is a serotonin subtype 3 (5-HT3) receptor antagonist indicated for:

• Moderately emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses (1.1)”

Evaluation: The term “serotonin subtype 3 (5-HT3) receptor antagonist” is used as the established pharmacologic class in the proposed labeling. The same term is used as the established pharmacologic class in the approved labeling for Aloxi® (palonosetron HCl) Injection. so it is appropriate for both products to share the same established pharmacologic class. The word “Capsules” should be deleted from this section.

Recommended Version:

“HIGHLIGHTS OF PRESCRIBING INFORMATION”

“INDICATIONS AND USAGE

4 pp withheld in full immediately after this page as (b)(4) Draft Labeling
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 90 to 173 times the human exposure (AUC= 49.7 ng·h/mL) at the recommended oral dose of 0.50 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 82 and 185 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 921 times the recommended human oral dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.”

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Nonclinical studies of palonosetron were reviewed under NDA 21,372. No nonclinical studies were submitted in the present application, as per an agreement between the Sponsor and the Division of Gastroenterology Products.

B. Pharmacologic activity

Palonosetron is a potent and selective 5-HT3 receptor antagonist that acts as an antiemetic.

C. Nonclinical safety issues relevant to clinical use

None.
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22,233

Review number: 1

Sequence number/date/type of submission: 000/October 22, 2007/Original

Information to sponsor: Yes (x) No ( )

Sponsor and/or agent: Helsinn Healthcare SA
Dr. Craig Lehmann
Lugano, Switzerland
August Consulting, Inc.
Austin, Texas

Manufacturer for drug substance: Helsinn Advanced Synthesis SA
Biasca, Switzerland

Reviewer name: David B. Joseph, Ph.D.

Division name: Gastroenterology Products

HFD #: 180

Review completion date: June 25, 2008

Drug:

- Trade name: ALOXI® (palonosetron HCl) Capsules
- Generic name: Palonosetron
- Code name: 08-PALO; RS-25259-197
- Chemical name: (3αS)-2,3,3a,4,5,6-Hexahydro-2-[(3S)-3-quinuclidinyl]-1H-benz[de]isoquinolin-1-one monohydrochloride
- CAS registry number: 135729-62-3
- Molecular formula/molecular weight: C_{19}H_{24}N_{2}O\cdot HCl/332.87

Structure:
**Relevant INDs/NDAs/DMFs:** IND 39,797 (palonosetron injection)/IND 42,886 (oral palonosetron)/NDA 21,372 (ALOXI® (palonosetron HCl) Injection)

**Drug class:** 5-HT₃ receptor antagonist/antiemetic

**Intended clinical population:** Patients receiving moderately emetogenic cancer chemotherapy

**Clinical formulation:** Soft gelatin capsules containing 0.56 mg palonosetron HCl, equivalent to 0.5 mg free base. The capsule ingredients are listed in the table below.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg/capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palonosetron HCl</td>
<td>0.56</td>
</tr>
<tr>
<td>Mono- and di-glycerides of Caprylic/Capric Acid</td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Glycerin,</td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Polyglyceryl olate</td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Purified water</td>
<td></td>
</tr>
<tr>
<td>Butylated hydroxyanisole</td>
<td>*</td>
</tr>
<tr>
<td>Butylated hydroxyanisole</td>
<td>*</td>
</tr>
<tr>
<td>proprietary to</td>
<td>*</td>
</tr>
</tbody>
</table>

**Route of administration:** oral

**Disclaimer:** Tabular and graphical information were constructed by the reviewer unless cited otherwise.

**Studies reviewed within this submission:** No preclinical studies were submitted, as per an agreement between the Sponsor and the Division of Gastroenterology Products (letter dated June 7, 2007 under IND 42,886). Preclinical studies were previously submitted and reviewed (Pharmacology/Toxicology review of NDA 21,372 dated July 11, 2003). The nonclinical section of this application contains only a summary of previously submitted studies.

**Studies not reviewed within this submission:** None.
2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Palonosetron is an antiemetic that acts through antagonism of 5-HT3 receptors. The drug reduces chemotherapy-induced vomiting in dogs and ferrets when administered before or after the emetic stimulus. Palonosetron is active through both intravenous and oral routes of administration. The antineoplastic actions of cancer chemotherapeutic drugs in tumor-bearing rodents were unaffected by palonosetron. No significant effects were observed in safety pharmacology studies of central nervous system function, circulatory function, respiration, renal function, or gastric emptying. Palonosetron produced inhibition of hERG and sodium channel currents (IKr and INa, respectively). In cardiac myocytes, IKr is the delayed rectifier potassium current involved in repolarization, whereas INa is a rapid inward current involved in depolarization. Inhibition of IKr and INa occurred only at drug concentrations that exceeded the expected human peak plasma levels by 10.8- and 2335-fold, respectively. Prolongation of action potential duration by palonosetron was observed in dog and rabbit Purkinje fibers, but only at concentrations over 100-times the expected human peak plasma levels. Intravenous administration of 1-1000 µg/kg in dogs had no significant effects on the mean QT or QTc values, compared to control values. However, the QT interval at 1000 µg/kg was increased by 0.05 sec over the pre-dose value in 5/6 dogs tested. Three dogs treated with 1000 µg/kg had QT intervals of 0.27-0.29 sec, whereas the normal range for QT intervals in dogs is 0.15-0.25 sec. A slight decrease in heart rate was also observed at 1000 µg/kg. Treatment of anesthetized rabbits with 10 mg/kg iv (approximately 1800-fold greater than the human intravenous dose) failed to produce Torsades des Pointes, although effects on cardiac conduction and arrhythmias were observed.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Palonosetron is a potent and selective 5-HT3 receptor antagonist. The pKi for 5-HT3 receptors in rat cerebral cortex was 10.4 ± 0.2 (Ki = 39.8 pM). Palonosetron was shown to bind to 5-HT3 receptors in brain regions involved in the vomiting reflex, including the nucleus tractus solitarius, and the chemoreceptor trigger zone in the area postrema. Other sites involved in the antiemetic effect of palonosetron include 5-HT3 receptors on vagal afferents. The vagal afferents provide input to the central emesis center (medulla) in response to serotonin release from enterochromaffin cells, which may be stimulated by chemotherapeutic agents.

Drug activity related to proposed indication: Oral dose levels of 0.01-0.1 mg/kg in dogs and 0.003-0.1 mg/kg in ferrets prevented cisplatin-induced emesis. Complete inhibition of cisplatin-induced emesis occurred at 0.1 mg/kg po in both species. Palonosetron reduces chemotherapy-induced vomiting in dogs and ferrets when administered before or after the emetic stimulus. The drug is active through both intravenous and oral routes of administration.

2.6.2.3 Secondary pharmacodynamics

No studies were submitted.
2.6.2.4 Safety pharmacology

No studies were submitted.

2.6.2.5 Pharmacodynamic drug interactions

No studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Palonosetron was rapidly absorbed following oral administration. Oral bioavailability was 6-13% in rats, dogs, and monkeys. The drug penetrated the blood-brain barrier and was concentrated in the small and large intestine. Elimination from tissues was generally correlated with elimination from plasma. Palonosetron was cleared primarily by hepatic metabolism. Plasma contained 10-12 metabolites after oral or intravenous administration in individual animal species. Two of the main metabolites in humans were shown to have weak activity at the 5-HT3 receptor, and are not expected to produce clinically relevant pharmacological activity. Excretion of radioactivity following oral administration of [14C]palonosetron in rats was 51% in urine and 41% in feces.

2.6.4.2 Methods of Analysis

Not applicable.

2.6.4.3 Absorption

No studies were submitted.

2.6.4.4 Distribution

No studies were submitted.

2.6.4.5 Metabolism

No studies were submitted.
2.6.4.6 Excretion

No studies were submitted.

2.6.4.7 Pharmacokinetic drug interactions

No studies were submitted.

2.6.4.8 Other Pharmacokinetic Studies

No studies were submitted.

2.6.4.9 Discussion and Conclusions

Not applicable.

2.6.4.10 Tables and Figures

Not applicable.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Single dose toxicity studies of palonosetron were performed in rats, mice, and dogs using intravenous and oral administration. The minimum intravenous lethal dose in rats and mice was 30 mg/kg. Intravenous administration of up to 20 mg/kg in dogs was not lethal. The minimum oral lethal dose was 500 mg/kg in rats and 100 mg/kg in dogs. Repeat-dose toxicity studies were performed in rats, mice, and dogs using intravenous and oral administration. The intravenous toxicology studies included a 1-month study in rats, a 6-month study in rats, a 1-month study in dogs, and a 9-month study in dogs. The oral toxicology studies included a 1-month study in rats, a 3-month study in rats, a 3-month study in mice, a 1-month study in dogs, and a 3-month study in dogs.

The no effect doses in the repeat-dose intravenous toxicity studies were in the range of 3 to 7 mg/kg/day. CNS appeared to be a target organ of toxicity in both rats and dogs, based on the incidence of convulsions, ataxia, and reduced activity. Vomiting and loose feces also occurred in dogs. In the 6-month intravenous study in rats, administration of 14 mg/kg/day produced convulsions, reduced activity, and death.
In the oral toxicity studies, palonosetron was tolerated at doses of up to 60 mg/kg/day in rats and mice (3-month studies) and 20-40 mg/kg/day in dogs (4-week and 3-month studies). Adverse effects in rats occurred at 120 and 180 mg/kg/day po (4-week and 3-month studies). The major effects included anemia, hepatocellular swelling and glycogen deposition, decreased bone marrow cellularity, decreased femoral trabecular bone, multiple lesions in testes, immature spermatogenic cells in the epididymis, atrophy of lymphoid tissues, and chronic nephrosis. In the 3-month rat study, oral administration of 180 mg/kg/day produced tremor, convulsions, and mortality.

Palonosetron was not tumorigenic at doses of 10, 30, and 60 mg/mg/day in a 104-week carcinogenicity study in mice. A carcinogenicity study in rats was performed using dose levels of 15, 30, and 60 mg/kg/day in males, and 15, 45, and 90 mg/kg/day in females. The plasma drug concentrations were higher in females. Palonosetron produced a number of neoplastic changes, primarily in endocrine organs. Increased incidences of benign pheochromocytoma were observed. The incidence of combined benign and malignant pheochromocytoma, pancreatic islet cell adenoma, combined incidences of islet cell adenoma and carcinoma, and adenoma of pars distalis was increased in males in the treatment groups. The incidence of hepatocellular adenoma and thyroid C-cell adenoma were increased in the high-dose females.

Palonosetron was negative in the Ames test, HGPRT mutation assay, mouse micronucleus assay, and the unscheduled DNA synthesis assay in rats. A positive result was observed in the chromosomal aberration test in CHO cells.

Palonosetron produced infertility in male rats, but only at 120 mg/kg/day po. No evidence of teratogenicity, embryo-fetotoxicity, or abnormal postnatal development was observed in reproductive studies using oral administration.

2.6.6.2 Single-dose toxicity

No studies were submitted.

2.6.6.3 Repeat-dose toxicity

No studies were submitted.

2.6.6.4 Genetic toxicology

No studies were submitted.

2.6.6.5 Carcinogenicity

No studies were submitted.

2.6.6.6 Reproductive and developmental toxicology

No studies were submitted.
2.6.6.7 Local tolerance

No studies were submitted.

2.6.6.8 Special toxicology studies

No studies were submitted.

2.6.6.9 Discussion and Conclusions

In repeat-dose oral toxicity studies, palonosetron was tolerated at doses of up to 60 mg/kg/day in rats and mice (3-month studies) and 20-40 mg/kg/day in dogs (4-week and 3-month studies). Adverse effects in rats occurred at 120 and 180 mg/kg/day po (4-week and 3-month studies). The major effects included anemia, hepatocellular swelling and glycogen deposition, decreased bone marrow cellularity, decreased femoral trabecular bone, multiple lesions in testes, immature spermatogenic cells in the epididymis, atrophy of lymphoid tissues, and chronic nephrosis. In the 3-month rat study, oral administration of 180 mg/kg/day produced tremor, convulsions, and mortality. The no effect doses in repeat-dose intravenous toxicity studies were in the range of 3 to 7 mg/kg/day. CNS appeared to be a target organ of toxicity in both rats and dogs, based on the incidence of convulsions, ataxia, and reduced activity. Vomiting and loose feces also occurred in dogs. In the 6-month intravenous study in rats, administration of 14 mg/kg/day produced convulsions, reduced activity, and death.

2.6.6.10 Tables and Figures

Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Palonosetron is a potent 5-HT3 receptor antagonist that acts as an antiemetic. Aloxi® (palonosetron HCI) Injection is approved for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy, prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, and prevention of postoperative nausea and vomiting for up to 24 hours following surgery. The present application is for an oral formulation of palonosetron HCI, Aloxi® Capsules. The proposed indication is the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
No nonclinical studies were submitted, as per an agreement between the Sponsor and the Division of Gastroenterology Products (letter dated June 7, 2007 under IND 42,886). A review of the nonclinical studies is found in the Pharmacology/Toxicology review of NDA 21,372 (Aloxi® Injection) dated July 11, 2003. The nonclinical section of the present application contains only a summary of the studies submitted in NDA 21,372. The nonclinical information is briefly summarized below. Although intravenous and oral toxicology studies of palonosetron are available, the toxicology summary will be limited to the oral studies, since these are more relevant to the safety of Aloxi Capsules.

Palonosetron is an antiemetic that acts through antagonism of 5-HT3 receptors. This drug prevents chemotherapy-induced vomiting in dogs and ferrets when administered before or after the emetic stimulus. Palonosetron is active through both intravenous and oral routes of administration. No significant effects were observed in safety pharmacology studies of central nervous system function, circulatory function, respiration, renal function, or gastric emptying. Palonosetron produced inhibition of hERG and sodium channel currents (I_{Kr} and I_{Na}, respectively). Inhibition of I_{Kr} and I_{Na} occurred only at drug concentrations that exceeded the expected human peak plasma levels by 10.8- and 2335-fold, respectively. Prolongation of action potential duration by palonosetron was observed in dog and rabbit Purkinje fibers, but only at concentrations over 100-times the expected human peak plasma levels. Administration of up to 1 mg/kg iv in dogs showed no effects on QTc interval, although QT was prolonged and heart rate was slightly decreased. Treatment of anesthetized rabbits with 10 mg/kg iv failed to produce Torsades des Pointes, although effects on cardiac conduction and arrhythmias were observed.

Palonosetron was rapidly absorbed following oral administration. Oral bioavailability was 6-13% in rats, dogs, and monkeys. The drug penetrated the blood-brain barrier and was concentrated in the small and large intestine. Elimination from tissues was generally correlated with elimination from plasma. Palonosetron was cleared primarily by hepatic metabolism. Plasma contained 10-12 metabolites after oral or intravenous administration in individual animal species. Two of the main metabolites in humans were shown to have weak activity at the 5-HT3 receptor, and are not expected to produce clinically relevant pharmacological activity. Excretion of radioactivity following oral administration of [14C]palonosetron in rats was 51% in urine and 41% in feces.

In the acute oral toxicity studies, the minimum lethal dose was 500 mg/kg in rats and 100 mg/kg in dogs. The repeat-dose oral toxicology studies included a 4-week study in rats, a 3-month study in rats, a 3-month study in mice, a 4-week study in dogs, and a 3-month study in dogs.

In the 4-week oral toxicity study in rats, palonosetron HCl was administered at 6, 18, 60, and 180 mg/kg/day. No treatment-related mortality was observed. A mild decrease in hemoglobin and other hematology parameters occurred in the 60 and 180 mg/kg/day groups. The identified target organs of toxicity in males were liver (increased weight, hepatocellular swelling, and glycogen deposition) and testes (degeneration/necrosis of the seminiferous epithelium and immature spermatogenic cells in the epididymis). In females, thymus was the identified target organ of toxicity, based on reduced weight, small size, and thymic lymphoid atrophy. The no effect dose was 18 mg/kg/day.
A 3-month oral dose range-finding study in rats was conducted with palonosetron HCl to provide a basis for dose selection in a 2-year oral carcinogenicity study. Dose levels of 0, 18, 60, 120, and 180 mg/kg/day were used. A dose-dependent suppression of bodyweight gain was seen among the males, and in the 120 and 180 mg/kg/day females. A reduction in testicular weights and accessory sex organs associated with diffuse testicular tubular atrophy (2/15 males), testicular aspermatogenesis (all males), and decreased spermatozoa in the epididymides (all males) was seen in the 180 mg/kg/day group. Lymphoid atrophy of the spleen was observed in 60% of the 120 mg/kg/day males. The MTD (maximum tolerated dose) in males was considered to be 60 mg/kg/day, based on slight suppression of bodyweight gain. The MTD in females was considered to be 120 mg/kg/day, based on slight suppression of bodyweight gain, slightly lower platelet counts, mild increases in absolute counts for leukocytes, neutrophils, and lymphocytes, increased triglycerides, increased weight of liver and spleen, and chronic nephrotic syndrome (36%, compared with none in the control group). The no effect dose in females was 60 mg/kg/day. Treatment of females with 180 mg/kg/day produced tremors, convulsions, and mortality in 6/15 animals tested. Effects in surviving females at the 180 mg/kg/day dose included alterations in hematology and clinical chemistry, and the following lesions: bone marrow toxicity (hypocellularity and reductions in femoral metaphysial trabecular bone), splenic lymphoid atrophy and necrosis, increased height of the follicular epithelium in thyroid, hypertrophy of the adrenal glomerulosa cells, and increased severity of chronic progressive necrosis and congestion of the liver.

The 3-month oral toxicity study in mice was conducted using dose levels of 0, 30, 60, 90, and 120 mg/kg/day palonosetron HCl (dose levels expressed as free base equivalent). Hypersalivation, convulsions, and deaths were observed in the 90 and 120 mg/kg/day groups. The drug produced a decrease in absolute weight of male reproductive organs, pulmonary congestion, and bleeding. Therefore lungs and male sex organs were identified as the target organs of toxicity in this study. At 60 mg/kg/day, only a minor change in absolute and relative weights of accessory sex organs was observed in the absence of histopathological alterations. Therefore this dose was considered as the MTD in males. The MTD in females was considered to 90 mg/kg/day, since no females died at this dose level.

In a 4-week oral toxicity study in dogs, palonosetron HCl was administered at doses of 2, 6, and 20 mg/kg/day. No treatment-related deaths occurred. Salivation (transient) was observed in the 6 and 20 mg/kg/day groups. Reductions in absolute and relative weights for testes were observed at the 20 mg/kg/day dose, without gross or histological correlates. No target organs of toxicity were identified, and the high-dose of 20 mg/kg/day was considered as the no effect dose.

A 3-month oral toxicity study in dogs was performed using doses of 0, 2, 10, and 40 mg/kg/day palonosetron HCl. The drug was administered in two divided doses. No target organs of toxicity were identified. Therefore, the no effect dose was 40 mg/kg/day.

A 2-year carcinogenicity study in rats was performed using oral dose levels of 0, 0, 15, 30, and 60 mg/kg/day in males, and 0, 0, 15, 45, and 90 mg/kg/day in females. The plasma drug concentrations were higher in females. Increased incidences of benign pheochromocytoma were observed in males. Increased incidences of combined benign and malignant pheochromocytoma, pancreatic islet cell adenoma, combined incidences of islet cell adenoma and carcinoma, and
adenoma of pars distalis were seen in males in the treatment groups. The incidence of hepatocellular adenoma and thyroid C-cell adenoma were increased in the high-dose females. Palonosetron was not tumorigenic at doses of 10, 30, and 60 mg/mg/day in a 104-week carcinogenicity study in mice.

Palonosetron was negative in the Ames test, HGPRT mutation assay, mouse micronucleus assay, and the unscheduled DNA synthesis assay in rats. A positive result was observed in the chromosomal aberration test in CHO cells. Palonosetron produced infertility in male rats, but only at 120 mg/kg/day po. No evidence of teratogenicity, embryo-fetotoxicity, or abnormal postnatal development was observed in reproductive studies using oral administration.

No effect dose levels were established in the oral toxicology studies of up to three months duration. The results of these studies support the safety of the proposed dose (0.56 mg palonosetron HCl, equivalent to 0.01 mg/kg in a 50-kg patient) and duration of treatment for Aloxi® Capsules. Further assurance of safety can be derived from the previous human experience with intravenous palonosetron (Aloxi® Injection).

Unresolved toxicology issues:

None.

Recommendations:

From a preclinical viewpoint, the application should be approved, with the provision that the “HIGHLIGHTS OF PRESCRIBING INFORMATION”, “Pregnancy” subsection, “OVERDOSAGE” section, and the “Carcinogenesis, Mutagenesis, Impairment of Fertility” subsection of the proposed labeling will be changed as described in the “EXECUTIVE SUMMARY” section of this review.

Suggested labeling: The labeling should be changed as described in the “EXECUTIVE SUMMARY” section of this review.
Reviewer Signature ____________________________________________
                        David B. Joseph, Ph.D.
                        Pharmacologist, HFD-180

Supervisor Signature ___________________________________________ Concurrence Yes ___ No ___
                        Sushanta K. Chakder, Ph.D.
                        Acting Pharmacology Team Leader, HFD-180

cc:
Orig NDA 22,233
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakder
HFD-180/Dr. Joseph

R/D Init.: S. Chakder 6/16/08

DJ/dbj: 6/25/08
C:\DATA\N22233806.0DJ

APPENDIX/ATTACHMENTS

None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Joseph
6/25/2008 09:31:00 AM
PHARMACOLOGIST

Sushanta Chakder
6/25/2008 02:15:39 PM
PHARMACOLOGIST