CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203050Orig1s000

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

Application number:	203050
Supporting document/s:	N/A
Applicant's letter date:	January 3, 2012
CDER stamp date:	January 3, 2012
Product:	Palonosetron Hydrochloride Injection
Indication:	For the prevention of acute and delayed nausea and vomiting associated with chemotherapy (CINV) and, postoperative nausea and vomiting (PONV) following surgery.
Applicant:	Dr. Reddy's Laboratories, Inc.
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	B. Emmanuel Akinshola, Ph.D.
Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Jagjit Grewal, M.P.H.

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1 Executive Summary

4.2 1.1 Recommendations

1.1.1 Approvability

From a nonclinical standpoint, the NDA is approvable.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

In this 505(b)(2) NDA submission, the sponsor did not submit any new nonclinical studies on palonosetron hydrochloride. The nonclinical sections of the labeling are adopted from the innovator's labeling of Aloxi (NDA 021372). Therefore, no changes in the proposed labeling are recommended.

4.3 1.2 Brief Discussion of Nonclinical Findings

No new toxicology studies were submitted under NDA 203050, but the toxicology studies conducted by the innovator have established the safety of palonosetron hydrochloride. Palonosetron is a serotonin (5-HT_3) receptor antagonist with a strong binding affinity for 5-HT_3 receptors, and is an antiemetic and antinauseant agent.

Palonosetron was non-mutagenic in the Ames test, the mammalian cell (Chinese hamster ovarian cell, CHO/HGPRT) forward mutation test, the *in vitro* hepatocyte unscheduled DNA synthesis test and the mouse micronucleus test. However, a clastogenic effect was observed in the Chinese hamster ovarian cell chromosomal aberration test.

Two year oral carcinogenicity studies were conducted in rats and mice by the innovator. In a 104-week oral gavage carcinogenicity study in Sprague-Dawley rats, palonosetron was administered at 15, 30 and 60 mg/kg/day in male rats and at 15, 45 and 90 mg/kg/day in female 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 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.

In a 104-week carcinogenicity study, CD-1 mice were treated with palonosetron by oral gavage at 10, 30 and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic in mice.

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 fetal malformations or visceral anomalies identified in rats and rabbits with dams given oral doses of palonosetron up to 60 mg/kg/day.

Pharmacologic Activity:

Palonosetron is a serotonin (5-HT_3) receptor antagonist with strong binding affinities for peripheral or central 5-HT_3 receptors. Palonosetron has been shown to prevent both acute and delayed emesis by prolonged inhibition of the 5-HT_3 receptor. In animal (rat, ferret, and dog) studies, palonosetron (RS 25259-197) was shown to dose-dependently inhibit the emesis reflex by selective blockade of the 5-HT_3 receptor.

2 Drug Information

2.1 Drug

Palonosetron Hydrochloride Injection

2.1.1 CAS Registry Number (Optional)

[135729-62-3]

2.1.2 Generic Name

Palonosetron Hydrochloride

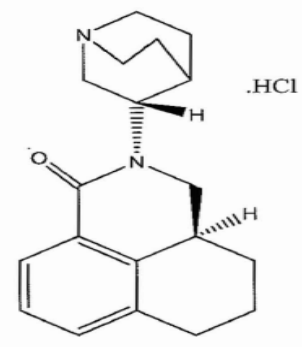
2.1.4 Chemical Name

(3aS)-2-[(S)-1-Azabicyclo [2.2.2] oct-3-yl]-2, 3,3a, 4, 5, 6-hexahydro-1oxo-1 Hbenz [de] isoquinoline hydrochloride.

2.1.5 Molecular Formula/Molecular Weight

$C_{19}H_{24}N_2O.HCl/332.87$

2.1.6 Structure



2.1.7 Pharmacologic class

Serotonin 5-HT3 receptor antagonist

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA 021372, (Aloxi) Helsinn Healthcare

2.3 Clinical Formulation

2.3.1 Drug Formulation

Palonosetron Hydrochloride Injection, 0.075 mg/1.5 ml and 0.25 mg/5 ml (b) (4) supplied as single (b) (4) vials.

Composition of Palonosetron Hydrochloride Injection, 0.075mg/1.5mL and 0.25 mg/5mL

S.No	Component	Qty (mg/mL)	Pharmaceutical Function
1.	Palonosetron Hydrochloride	(b) (4)	Active Pharmaceutical ingredient
2.	Mannitol (b) (4) USP		(b) (4)
3.	Sodium acetate trihydrate USP		
4.	Water for Injection USP		
5.	Sodium hydroxide NF	q.s to adjust the pH 4.5 to 5.5	For pH adjustment
6.	Hydrochloric acid NF	q.s to adjust the pH 4.5 to 5.5	For pH adjustment
			(b) (4)

* (b) (4) Palonosetron Hydrochloride is equivalent to 0.05 mg of Palonosetron base.
q.s – quantity sufficient.

2.3.2 Comments on Novel Excipients

There are no novel excipients in the drug product.

2.3.3 Comments on Impurities/Degradants of Concern

Four (b) (4) impurities were identified in the manufacturing process for palonosetron hydrochloride: (b) (4) The levels of these impurities were controlled to a limit not more than (b) (4) % each in the final drug substance. The levels of other unidentified impurities were controlled to not more than (b) (4) %. The total level of all impurities was controlled to a level not more than (b) (4) %.

The following potential residual solvents in the manufacturing process were controlled at not more than the indicated levels: (b) (4) The indicated residual solvent levels are within the recommended ICH limits.

2.4 Proposed Clinical Population and Dosing Regimen

The proposed indication for Palonosetron hydrochloride injection is in the prevention of acute and delayed nausea and vomiting associated with the initial and repeat courses of cancer chemotherapy (CINV) administration in patients. Palonosetron hydrochloride injection is also proposed for use in the prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery.

2.5 Regulatory Background

None

3 Studies Submitted

No non-clinical studies were submitted in this 505(b)(2) application.

3.1 Studies Reviewed

The sponsor submitted several published studies on palonosetron hydrochloride. Relevant publications were reviewed.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.4 Primary Pharmacology

Palonosetron exhibits unique molecular interactions with the 5-HT_3 Receptor. Camilo Rojas et al., *Anesth Analg*. 107(2):469-478, 2008.

Receptor site saturation binding experiments (in HEK 293 cells expressing the 5-HT_3 receptor) were performed with [3H] palonosetron, granisetron, and ondansetron to examine competitive versus potential allosteric interactions between the receptor antagonists and the 5-HT_3 receptor.
Palonosetron showed allosteric binding and positive cooperativity in binding to the 5-HT_3 receptor. The result of the binding assay demonstrated that [^{3}H] palonosetron has a higher affinity for the serotonin receptor with a kd value of 0.2 nM, when compared to kd values of 1 nM for granisetron, and 6 nM for ondansetron.

Palonosetron triggers 5-HT_3 Receptor internalization and causes prolonged inhibition of receptor function. Camilo Rojas et al., Eur. J. Pharmacol. 626(2-3):193-199, 2010.

This study shows that palonosetron uniquely triggers 5-HT_3 receptor internalization to induce prolonged inhibition of receptor function. Following 24 h incubation of [^{3}H] palonosetron with human embryonic kidney (HEK) cells, and washing of excess radioactivity from the incubation mixture, [^{3}H] palonosetron remained associated with whole cells, but not cell-free membranes. [^{3}H] palonosetron binding to cells was resistant to both protease and acid treatments designed to denature cell surface proteins, suggesting that the receptor complex was inside the cells rather than at the surface. Cells pretreated with unlabeled palonosetron subsequently exhibited reduced cell surface 5-HT_3 receptor binding.

Palonosetron-triggered receptor internalization was visualized by confocal fluorescence microscopy using HEK 293 cells transfected with 5-HT_3 receptor fused to enhanced cyan fluorescent protein. In contrast, granisetron and ondansetron showed minimal to no effect on receptor internalization or prolonged inhibition of receptor function.

Pharmacological characterization of RS 2529-197, a novel and selective 5-HT_3 receptor antagonist, *in vivo.* R.M. Eglen et al., Br.J. Pharmacol. 114(4):860-866, 1995.

In animal (rat, ferret, and dog) studies, Palonosetron (RS 25259-197) was shown to inhibit the emesis reflex by selective blockade of the 5-HT_3 receptor. Male Sprague Dawley (250-380 g) rats were administered RS 25259-197 by the intravenous (I.V.), intraduodenal (I.D.) or transdermal routes. RS 25259-197 dose-dependently inhibited the vagal reflex bradycardia (Von Bezold-Jarisch reflex) induced by 2-methyl 5-HT. RS 25259-197 was more potent (ID_{50} = 0.04 µg/kg I.V., 3.2 µg/kg I.D. and 32.8 µg/kg per chamber) and exhibited a longer duration of action than either ondansetron or granisetron.

In conscious male ferrets (1-1.4 kg), oral (P.O.) or I.V. RS 25259-197 dose-dependently (1.1 µg/kg, I.V. and 3.2 µg/kg P.O.) inhibited cisplatin-induced emesis. RS 25259-197 was more potent than ondansetron and equipotent with granisetron in this respect.

In conscious adult male dogs (8-20 kg), I.V. or P.O. administered RS 25259-197 dose-dependently inhibited emesis induced by cisplatin (ID_{50} = 1.9 µg/kg I.V., and 8.5 µg/kg P.O.), dacarbazin (ID_{50} = 4.1 µg/kg I.V., and 9.7 µg/kg P.O.), actinomycin D (ID_{50} = 4.9 µg/kg I.V., and 2.5 µg/kg P.O.) and mechlorethamine (ID_{50} = 4.4 µg/kg I.V., and 3.0 µg/kg P.O.). RS 25259-197 was much more potent than ondansetron against each of the emetogenic agents. When tested at equally effective I.V. doses against cisplatin-induced emesis in dogs, RS 25259-197 had a longer duration of anti-emetic activity (7 hours) than ondansetron (4 hours).

The antiemetic 5-HT_3 receptor antagonist palonosetron inhibits substance P-mediated responses in vitro and in vivo. C. Rojas et al., J Pharmacol Exp Ther. 335(2):326-368, 2010.

The effect of palonosetron on the neuronal response to substance P (10 µg/kg) was measured in the autonomic nodose ganglion of rats that were previously administered cisplatin (5 mg/kg I.P.). Cisplatin is known to trigger the release of serotonin from enterochromaffin cells, which in turn activates 5-HT_3 receptors located on the surface of vagal afferents. Intravenous infusion of palonosetron, (30, 100, and 300 µg/kg) but not ondansetron or granisetron, dose-dependently inhibited cisplatin-induced substance P impulse response measured in the rat nodose ganglion. Palonosetron (300 µg/kg) blocked substance P impulse response in the nodose ganglion by 33 ± 7 % (when infused 30 min before cisplatin), by 70 ± 8 % (when infused 5 hr after cisplatin), and by 78 ± 10 % (when infused 10 hr after cisplatin).

4.5 Secondary Pharmacology

No secondary pharmacology studies were submitted.

4.3 Safety Pharmacology

Pharmacological characterization of RS 2529-197, a novel and selective 5-HT_3 receptor antagonist, *in vivo.* R.M. Eglen et al., Br.J. Pharmacol. 114(4):860-866, 1995.

The effects of RS 25259-197 (palonosetron) on cardiovascular functions were studied in dogs, at doses that showed antiemetic activity. Anesthetized male and female mongrel dogs (11-16 kg) were administered vehicle or single dose of RS 25259-197 (10, 100, and 1000 µg/kg I.V.). Mean arterial pressure (MAP), cardiac output (CO), blood pressure dynamics (dP/dT) and heart rate (HR) were measured immediately prior to dosing and at 2, 5, 15, 30, 45, and 60 min after each dose of RS 25259-197. Baseline values for the measured parameters did not differ significantly between the vehicle and RS 25259-197 treatment groups. The administration of vehicle or RS 25259-197 had no significant effects on MAP, CO, dP/dT and HR. RS 25259-197 produced a significant decrease in heart rate at 1000 µg/kg I.V., only at 45 min post-treatment. However, since the antiemetic effect of RS 25259-197 in dogs were observed at doses as low as one µg/kg, the test article is essentially devoid of any adverse cardiovascular side-effects at doses that produced anti-emetic effects.

5 Pharmacokinetics/ADME/Toxicokinetics

No pharmacokinetics/toxicokinetics 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 reproductive and developmental toxicology studies were submitted.

10 Special Toxicology Studies

No special toxicology studies were submitted.

11 Integrated Summary and Safety Evaluation

In this 505(b)(2) NDA submission, the sponsor is seeking approval of palonosetron hydrochloride injection (0.075 mg/1.5 ml and 0.25 mg/5 ml) for the prevention of acute and delayed nausea and vomiting associated with the initial and repeat courses of cancer chemotherapy (CINV), and for the prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. No new nonclinical studies were submitted, but the sponsor submitted published nonclinical studies on palonosetron and also referenced NDA 021372 for Aloxi.

Palonosetron is a serotonin (5-HT_3) receptor antagonist with a strong binding affinity for 5-HT_3 receptors. Palonosetron acts by inhibiting serotonin from activating the 5-HT_3 receptors and initiating the nausea and vomiting response.

The pharmacological and toxicological properties of palonosetron have been studied extensively by the innovator. In published *in vitro* binding studies in HEK 293 cells expressing 5-HT_3 receptors, palonosetron was shown to possess a higher binding affinity for the serotonin (5-HT) receptors than ondansetron or granisetron. Palonosetron was also shown to trigger 5-HT_3 receptor internalization in HEK 293 cells, in contrast to ondansetron or granisetron. Receptor internalization was suggested as a mechanism of prolonged inhibition of the 5-HT_3 receptors by palonosetron to prevent both acute and

delayed emesis. Studies in rats, ferrets and dogs have shown that palonosetron was more potent in inhibiting the emesis reflex for a longer duration than ondansetron or granisetron. Palonosetron did not show any adverse cardiovascular effects in anesthetized mongrel dogs at doses as high as 1000 µg/kg

Toxicology studies conducted by the innovator in different species have established the nonclinical safety of palonosetron hydrochloride.

Palonosetron was not genotoxic in the Ames test, the mammalian cell (Chinese hamster ovarian cell, CHO/HGPRT) forward mutation test, the unscheduled DNA synthesis test and the mouse micronucleus test. However, it was found to be clastogenic in the CHO cell chromosomal aberration test.

In a 104-week oral gavage carcinogenicity study in Sprague-Dawley rats, palonosetron was administered at 15, 30 and 60 mg/kg/day in male rats and at 15, 45 and 90 mg/kg/day in female rats. Treatment with palonosetron resulted in increased incidences of adrenal pheochromocytoma, increased incidences of pancreatic islet cell adenoma, pituitary adenoma and combined adenoma and carcinoma 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.
In a 104-week carcinogenicity study, CD-1 mice treated with palonosetron by oral gavage at 10, 30 and 60 mg/kg/day did not develop tumors.

Palonosetron treatment did not affect fertility or reproductive performance in rats at oral doses up to 60 mg/kg/day. There were no fetal malformations or visceral anomalies identified in rats and rabbits with dams given oral doses of palonosetron up to 60 mg/kg/day.

In conclusion, palonosetron hydrochloride injection (Aloxi) is an approved drug product for the prevention of nausea and vomiting associated with treatments of emetogenic chemotherapy or surgery. The difference in formulation between the proposed palonosetron hydrochloride injection and the reference product (Aloxi) is the change in some excipients - (b) (4) sodium acetate trihydrate is substituted (b) (4) There are no safety concerns for the new formulation of palonosetron hydrochloride.

12 Appendix/Attachments

None

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/s/

BABATUNDE E AKINSHOLA
09/13/2012

SUSHANTA K CHAKDER
09/13/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:
NDA 203050

Applicant: Dr. Reddy's Laboratories Limited

Stamp Date: January 3, 2012

Drug Name: Palonosetron Hydrochloride Injection

NDA/BLA Type: 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A No non-clinical studies were conducted
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

BABATUNDE E AKINSHOLA
02/15/2012

SUSHANTA K CHAKDER
02/15/2012