

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-372/S008/S010

MEDICAL REVIEW(S)

**Division of Gastroenterology Products
Clinical Review**

Application Type NDA 21-372/S008, (b) (4) S010
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Drug Aloxi® Palonosetron
Therapeutic Class 5HT³ Receptor Antagonist

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Priority Designation S
Formulation Intravenous
Dosing Regimen 0.075 mg

Indication(s) Post operative nausea and vomiting (PONV):
(b) (4)

Intended Population Adults

Reviewer Dr. Nancy F. Snow
Medical Officer
HFD-180

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical standpoint, approval of this application, with modifications, is recommended. The sponsor has applied for two indications: prevention of postoperative nausea and vomiting (PONV) for up to (b) (4) (b) (4). The sponsor is also requesting removal of QTc prolongation warning information from the **Warnings and Precautions** section of the product labeling.

In two randomized, phase 3 clinical studies (PALO-04-06 and PALO-04-07), at single doses of 0.025, 0.050 or 0.075 mg, palonosetron was compared with placebo for the prevention of PONV (b) (4) 1090 patients undergoing laparoscopic abdominal or gynecological surgery (04-06) or gynecological or breast surgery (04-06).

The sponsor defines PONV as nausea and vomiting that occur from 0 to 6 hours postoperatively, while patients are in a post-operative, monitored setting. (b) (4)
(b) (4)

Smaller doses of palonosetron than the dose currently approved for CINV (0.25 mg) were studied in Phase 3 clinical trials, and administration of the study drug was on a one time basis, prior to the induction of anesthesia. Adverse events were minimal, and comparable to those attributed to Aloxi® in previous CINV trials. In addition to pivotal and supporting studies for the two above-mentioned indications, the sponsor submitted a thorough QT study (tQT) which demonstrated that at doses as high as 2.25 mg; a dose ~ 30 times higher than the intended PONV (b) (4) dose of 0.075 mg, palonosetron did not have a significant effect on the QT interval.

Two co-primary endpoints (discussed in detail in section 6.1.2 of this review) were used for the PONV (b) (4) indications; complete response (CR) from 0 to 24 hours, and CR from 24 to 72 hours. Relevant secondary endpoints, which looked at CR at additional time intervals, were also considered.

Results from pivotal study PALO-04-06 demonstrated a therapeutic benefit over placebo for the proposed 0.075 mg palonosetron dose for the time interval 0 to 24 hours. This dose level, however, failed to demonstrate significant advantage over placebo in achieving CR from 24 to 72 hours (i.e., the co-primary endpoint was not met).

A second study, PALO-04-07, originally designed as a pivotal study, was submitted as a supportive study due to potential unblinding of the first 130 patients. The FAS (full analysis set) used for a sensitivity analysis of the two co-primary efficacy variables showed that there was an

advantage over placebo for all palonosetron doses from 0 to 24 hours, and for the 0.075 mg dose for the 24 to 72 hour time period. Results of PALO-04-07 provided some support for the findings of PALO-04-06, although the potential unblinding limits the utility of the trial.

The sponsor's request to remove QT warning information from the label is based upon favorable results from an ICH compliant thorough QT study in which doses of palonosetron as high as 2.25 mg failed to demonstrate significant effects on the QT interval

Therefore, the following are conclusions regarding the two proposed indications, and removal of QT warning information from the product label:

- PONV; Efficacy and safety are shown for the 0 to 24 hour time period, but efficacy was not shown for the period beyond 24 hours (i.e., 24 to 72 hours)
- [REDACTED] (b) (4)
- Adverse events were minimal, and comparable to those attributed to Aloxi® in previous CINV trials
- Periodic post-marketing safety reviews have not identified new adverse reactions of concern or new safety signals related to palonosetron administration
- Removal of QT warning; some changes to the label are acceptable based on the tQT study. These will be addressed in labeling negotiations with the sponsor.

1.2 Recommendation on Post marketing Actions

From a clinical standpoint, no post marketing actions are recommended.

1.2.1 Risk Management Activity

From a clinical standpoint, risk management activity is not recommended.

1.2.2 Required Phase 4 Commitments

From a clinical standpoint, no Phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Two Phase 3 trials, PALO-04-06 and PALO-04-07, and Phase 2 study 2500, evaluated the clinical efficacy and safety of I.V. palonosetron, when administered before surgery to prevent PONV (b) (4)

One of the Phase 3 trials (PALO-04-06) is considered pivotal; the others (PALO-04-07), and study 2500, are confirmatory. The palonosetron PONV (b) (4) development program did not include any Phase 1 studies specifically designed as part of the demonstration of efficacy and safety in PONV (b) (4)

Three Phase 1 trials conducted in association with the CINV indication are part of the sNDA submission because they were conducted after the approval of CINV, and provide important data for an understanding of palonosetron. Two studies in healthy volunteers evaluated drug-drug interactions; the third was an E14 compliant thorough QT/QTc study. Information from all 4 PONV clinical trials, including I.V. and oral administration, is considered in the safety evaluation of palonosetron for PONV (b) (4)

1.3.2 Efficacy

As noted, this application is filed in support of a single I.V. dose of palonosetron for the following indications: prevention of post-operative nausea and vomiting (PONV), (b) (4) for up to (b) (4)

PONV is defined by the sponsor as nausea and vomiting that occur from 0 to 6 hours postoperatively, while the patient is in a post-operative, monitored setting. (b) (4)

Three clinical studies provide data for the efficacy review to support the PONV (b) (4) indications being sought. These include pivotal study PALO-04-06, and supportive studies PALO-04-07 and 2500. The Phase 3 studies (PALO-04-06 and PALO-04-07) are double-blind, randomized investigations of palonosetron 0.025 mg, 0.050 mg or 0.075 mg given as a single I.V. bolus within 5 minutes prior to anesthesia induction, compared to placebo. The objective of these studies is to demonstrate superiority of at least one of the three palonosetron doses evaluated, over placebo.

Of the two proposed indications, PONV (b) (4) only PONV was specified in the original protocol. In PALO-04-06, for the 0 to 24 hour time period (b) (4) (b) (4) alonoseetron demonstrated a distinct therapeutic advantage over placebo for the 0.050 mg (prevention gain 13.5%) and 0.075 mg (prevention gain 16.8%) dose

levels. Significant p-values were obtained for palonosetron 0.050 mg ($p=0.017$), and 0.075 mg ($p=0.0035$). No significant p-values were observed for the 0.025 mg dose.

For the time interval 24 to 72 hours, significant benefit over placebo was not shown for any dose level, and all p-values exceeded the pre-set adjusted significance levels. Thus for the PONV (b) (4) (b) (4) indications, efficacy was seen in the 0 to 24 hour time frame, but not the 24 to 72 hour time interval.

Medical Officer's Comments:

As noted, efficacy conclusions are drawn from study PALO-04-06. PALO-04-07 is supportive only due to potential unblinding. In PALO-04-06, for the 0 to 24 hour time period, palonosetron demonstrated a distinct therapeutic advantage over placebo for the 0.050 mg (prevention gain 13.5%) and 0.075 mg (prevention gain 16.8%) dose levels. Significant p-values were obtained for palonosetron 0.050 mg ($p=0.017$), and 0.075 mg ($p=0.0035$). No significant p-values were observed for the 0.025 mg dose versus placebo.

In the pivotal study, for the proposed indications, significant benefit over placebo was not shown for any dose level during the time interval 24 to 72 hours, since all p-values exceeded the pre-set adjusted significance levels.

1.3.3 Safety

The palonosetron PONV, (b) (4) safety database is comprised of safety data from 1952 subjects enrolled in four clinical trials, in which 1520 patients received palonosetron. In addition to safety information from pivotal and supporting studies, information on the effects of palonosetron on cardiac conduction (QTc) was submitted in thorough QT study PALO-03-11.

No new safety findings emerged from the PONV development program or post marketing surveillance which changes the risk profile of palonosetron since original FDA approval of the drug in 2003.

The most common adverse reactions were constipation, flatulence, abdominal pain, headache and dizziness. Incidences of these events were similar across all palonosetron dose groups, and comparable to placebo, except headache, whose incidence was higher in the highest dose group (>0.075 mg), a dose level not used in the Phase 3 trials.

Thorough QT/QTc (tQT) study PALO-03-11 showed that palonosetron is not associated with significant QT prolongation at doses up to 2.25 mg, thus providing a 30-fold safety margin for the proposed PONV (b) (4) dose, 0.075 mg, and a 9-fold safety margin for the FDA approved CINV dose, 0.25 mg. Information from the ECG analysis performed in association with Phase 3 PONV trials showed no differences in ECG parameters between palonosetron and placebo-treated subjects, further supporting the tQT findings

The most commonly reported adverse events that were possibly or probably related to treatment were constipation and headache, followed by QT prolongation, bradycardia and pruritis. Constipation was seen in 3% of patients receiving palonosetron 0.025 mg, 4% of patients receiving palonosetron 0.050 mg, 2% of patients receiving palonosetron 0.075 mg, and 3% of patients receiving placebo. Likewise, headache was noted in 5% of the 0.025 mg dose group, 4% of the 0.050 mg dose group, 3% of the 0.075 mg dose group, and 4% of the placebo group. In summary, a clear cut dose response or differences between palonosetron and placebo was not seen. Further analysis of QT data is included in section 7.1.9 of this review.

Overall, the clinical data submitted in this efficacy supplement appear to support the safe use of palonosetron as a one-time dose to prevent post-operative (b) (4) nausea and vomiting for up to 24 hours after surgery.

1.3.4 Dosing Regimen and Administration

The doses of palonosetron selected for Phase 3 PONV studies were based on results of Phase 2 dose-ranging studies 2500 and 2502. In Study 2500, a single I.V. dose of palonosetron was administered to surgical patients at one of five dose levels (0.1 µg/kg, 0.3 µg/kg, 1 µg/kg, 3 µg/kg or 30 µg/kg) or placebo. In Study 2502, surgical patients were administered a single oral dose of palonosetron at one of five dose levels (0.3 µg/kg, 1 µg/kg, 3 µg/kg, 10 µg/kg or 30 µg/kg) or placebo.

Prior studies in healthy volunteers demonstrated that palonosetron was well tolerated, had generally dose proportional pharmacokinetics, and a mean half-life on the order of 40 hours. Phase 2 studies showed antiemetic effects in PONV patients (at doses ranging from 0.1 µg/kg to 30 µg/kg), and provided information for dose selection and additional safety support for continued Phase 3 development.

The proposed PONV (b) (4) market dose for I.V. palonosetron, 0.075 mg, is more than 3-fold lower than the currently approved CINV dose, approximately 80-fold lower than the highest dose (90 µg/kg) used in Phase 2 CINV study 2330, and approximately 28-fold lower than the maximum dose (30 µg/kg) used in Phase 2 studies in the target PONV patient population. A dose of 2.25 mg, used in thorough QT study PALO-03-11, is 30 fold greater than the proposed PONV (b) (4) dose.

1.3.5 Drug-Drug Interactions

The time to recovery during surgery was collected and analyzed in the two Phase 3 trials PALO-04-06 and PALO-04-07 to provide a clinical indication of whether palonosetron might have an interaction with anesthetic agents. In study PALO-04-06, the mean (SD) recovery time for placebo patients was 9.8 min (10.2), while that of the palonosetron treated patients was 11.8 min (12.2), 9.4 min (12.8) and 12.4 min (16.7), after 0.025 mg, 0.050 mg and 0.075 mg, respectively.

Likewise in PALO-04-07 there were no significant differences between placebo and palonosetron treated patients in the time to recovery after surgery, and indicate that a single dose

of palonosetron at 0.025 mg, 0.05 mg, or 0.075 mg would not be likely to interact with anesthetic agents or other drugs used intra- or perioperatively.

Drug interaction studies in healthy volunteers demonstrated that single doses of palonosetron do not significantly affect pharmacokinetic parameters of metoclopramide or dexamethasone, and vice-versa. Although less relevant for the PONV (b) (4) indications, metoclopramide and dexamethasone may be used, along with palonosetron, for the prevention of CINV.

In an interaction study of palonosetron and aprepitant, 0.25 mg of palonosetron was administered as an I.V. bolus alone or co-administered with aprepitant to healthy subjects. Aprepitant did not affect the AUC_{0-∞} of palonosetron but did increase its C_{max} by 15%, with the 90% CI of bioequivalence comparison being 61.8% to 157%, which is outside the bioequivalence acceptance criteria of 80% to 125%. Adverse events were similar in both treatments.

The biopharmaceutics reviewer, medical reviewer, and sponsor conclude that co-administration of aprepitant with palonosetron is acceptable. From a safety perspective, the increase in C_{max} does not appear to be clinically meaningful.

In-vitro studies indicate that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5, nor does it induce the activity of CYP1A2, CYP2D6 or CYP3A3/4. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low.

Medical Officer's Comment:

The drug-drug interaction studies are valuable in elucidating the activity of palonosetron with anesthetic agents, metoclopramide, dexamethasone, and aprepitant. The later three are drugs that may be used with palonosetron for the prevention of CINV, but would not be used for prevention of PONV (b) (4)

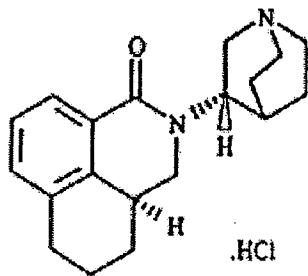
1.3.6 Special Populations

Palonosetron has not been studied in pediatric populations, the approved label does not recommend dose adjustments for special populations, and the current submission does not provide new information on the use of palonosetron in special populations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Trade Name (established name): Aloxi® (Palonosetron Hydrochloride)



Chemical name/empirical formula:

- (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[de]isoquinoline hydrochloride
- C₁₉H₂₄N₂O.HCl

Proposed Indication:

The prevention of postoperative (b) (4) nausea and vomiting (PONV) (b) (4) or up to (b) (4)

Proposed Age group: Adults ≥ 18

Pharmacologic Class: Selective serotonin subtype 3 (5HT₃) receptor antagonist

Route of administration, Description, and Formulation: Intravenous injection

Proposed Treatment Regimen: 0.075 mg administered as a single dose injected intravenously as a bolus, over 10 seconds, immediately before the induction of anesthesia

2.2 Currently Available Treatment for Indications

Three drug products in the 5HT₃ receptor antagonist class are available for the indication of post-operative nausea and vomiting (PONV). These include; ondansetron, granisetron and dolasetron.

(b) (4)

2.3 Availability of Proposed Active Ingredient in the United States

Palonosetron, initially approved for use in the United States in July 2003, is currently indicated for the prevention of acute chemotherapy induced nausea and vomiting (CINV) associated with highly and moderately emetogenic chemotherapy regimens, and delayed CINV associated with moderately emetogenic chemotherapy. Palonosetron is approved for use in 53 countries worldwide.

2.4 Important Issues with Pharmacologically Related Products

In 2006 the FDA Division of Drug Risk Evaluation (DDRE) conducted a review of the Adverse Event Reporting System (AERS) for cases of selected cardiovascular events associated with ondansetron, granisetron, dolasetron, and palonosetron use. Based on those results, the DDRE concluded that cardiovascular AEs are adequately reflected in the labels for ondansetron, granisetron, dolasetron, and palonosetron.

At a November 16, 2006 Pediatric Advisory Committee (PAC) meeting the FDA reported on the one year post-exclusivity AE review for ondansetron. In the report pediatric deaths pre and post exclusivity were examined. Of 14 unduplicated cases, 7 were excluded due to confounding or insufficient information, and 7 were confounded by serious underlying medical conditions. In the post-exclusivity period 1 death case had insufficient information to assess causality. Continued monitoring of ondansetron for adverse events in all populations was recommended.

Medical Officer's Comment:

The PAC addressed pediatric deaths associated with ondansetron, which is approved for pediatric use. Palonosetron is not approved for pediatric use at this time.

2.5 Presubmission Regulatory Activity

Syntex Laboratories, the original sponsor, filed the first IND for Palonosetron on 2 June 1992 (IND 39.797) for the I.V. formulation [REDACTED]

(b) (4)
(b) (4)

[REDACTED] (b) (4) Helsinn Healthcare SA assumed responsibilities for both I.V. and oral INDs on 3 August 1998. The following Table 1 (included in the sponsor's sNDA submission) provides a brief overview of regulatory events pertaining to efficacy in the PONV program.

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 NDA 21-372/S-008
 Palonosetron, Aloxi®

Table 1
Palonosetron PONV Regulatory History

Outcome of Meeting/Agreement	
End-Phase 2 Meeting 5/4/03	Agreed that the two Phase 3 efficacy protocols, PALO-04-06 and PALO-04-07 appeared adequate to pivotally support a label claim for the prevention of PONV. Commented in end of phase 2 meeting minutes regarding the design of treatment allocation schemes and patient populations for these two trials and indicated that the overall planned design, objectives, efficacy endpoints, sample size and planned statistical analysis were acceptable.
FDA SPA of Phase 3 efficacy protocols; FDA Letters dated Dec. 17, 2004, March 7-8 2005	FDA agreed that the overall protocol design, sample size, outlined execution, and analyses of these pivotal protocols were acceptable as presented.
Teleconference: Clinical supply label January 2006	A subset of patients was potentially unblinded by an issue in clinical supply labeling. FDA agreed that totally replacing the potentially affected 130 patients in Study PALO-04-07 was acceptable.
Teleconference: Potential unblinding at German sites Oct. 13, 2006	A second episode, identified after enrollment was complete, involved misapplication of labeling to the drug accountability form at 12 German sites. FDA determined that PALO-04-07 may serve as a supporting study for purposes of the planned PONV sNDA based on this potential unblinding. Further statements regarding the potential unblinding issue were obtained by a third party from affected sites. A sensitivity analysis on the primary efficacy endpoint has been performed and is included in the PALO-04-07 report as discussed with FDA.
Pre-NDA Meeting Dec. 7. 2006	Based on preliminary Phase 3 efficacy results for pivotal trial PALO-04-06, confirmatory efficacy results from Phase 3 trial PALO-04-07, and Phase 2 trial 2500, FDA concluded the NDA appeared ready for submission.

Medical Officer's Comment:

The palonosetron regulatory history did not initially include

(b) (4)

(b) (4)



2.6 Other Relevant Background Information

N/A

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

N/A

3.2 Animal Pharmacology/Toxicology

Since palonosetron is already approved, no further pre-clinical studies were required. Animal Pharmacology/Toxicology studies are reviewed in the original NDA submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data is provided by the sponsor in a multiple volume paper submission. Further clinical data is derived from trials in support of the original NDA approval, and post-marketing safety data.

4.2 Tables of Clinical Studies

Table 2 provides a description of pivotal and confirmatory trials used to support this submission.

Table 2; Table of Clinical Studies for NDA 21-372/S008, (b) (4)S010

Table 8.S.2:1 Controlled Clinical Trials

Study Number Study Dates Study Centers	Study Design	Comparator	No. of Subjects: (enrolled/analyzed/FAS ^a /PF ^b) Age Range ^c Sex Distribution ^b	FAS ^a Dose Groups
A. Pivotal PONV Efficacy and Safety Study				
PALO-04-06 May 2005 – June 2006 43 centers in the U.S. and Romania	Randomized, double-blind, multicenter, parallel-group, balanced, stratified phase 3 efficacy and safety study of single IV doses of palonosetron versus placebo in outpatients to prevent postoperative nausea and vomiting following elective abdominal or gynecological laparoscopic surgery.	Placebo	574/547/546/344 18-77 years 23 M; 523 F	Palonosetron 0.025 mg: 136 Palonosetron 0.050 mg: 137 Palonosetron 0.075 mg: 138 Placebo: 135
B. Confirmatory Trials				
PALO-04-07 August 2005 – May 2006 28 centers in Europe (Germany, Poland, Czech Republic)	Randomized, double-blind, multicenter, parallel-group, balanced, stratified phase 3 efficacy and safety study of single IV doses of palonosetron versus placebo to prevent postoperative nausea and vomiting following elective gynecological or breast surgery.	Placebo	694/673/MFAS 544; PFAS 369/288 18-86 years 0 M; 673 F	Palonosetron 0.025 mg: 88 PFAS; 136 MFAS Palonosetron 0.050 mg: 96 PFAS; 137 MFAS Palonosetron 0.075 mg: 95 PFAS; 135 MFAS Placebo: 90 PFAS; 136 MFAS
Study 2500 ^d February – November 1994 5 centers in the U.S.	Randomized, double-blind, multicenter, placebo-controlled, phase 2, dose-ranging efficacy, safety, and pharmacokinetics study of four dose levels of IV palonosetron to prevent postoperative nausea and vomiting following abdominal or vaginal hysterectomy.	Placebo	381/381/372 ^e 24-80 years 0 M; 372 F	Palonosetron 0.1 µg/kg: 47 Palonosetron 0.3 µg/kg: 67 Palonosetron 1 µg/kg: 62 Palonosetron 3 µg/kg: 67 Palonosetron 30 µg/kg: 67 Placebo: 62

^aPALO-04-07 – due to events which occurred in this study a modified full analysis set (MFAS) and a primary full analysis set (PFAS) were created. The MFAS is a subset of the FAS. The PFAS is a subset of the MFAS.

^bBased on the Full Analysis Set (FAS) population for PALO-04-06 and PALO-04-07 and the evaluable patients for Study 2500

^cStudy 2500 contained an Enrolled, Analyzed and an evaluable patient population

4.3 Review Strategy

A review of the efficacy of palonosetron for prevention of PONV (b) (4) is based primarily on pivotal study PALO-04-06, and to some extent on Study 2500. Study PALO-04-07 provides data of limited utility due to potential unblinding. Safety data are obtained from Phase 2 and 3 studies, thorough QT study PALO-03-11, post-marketing data, and safety data from the CINV application.

4.4 Data Quality and Integrity

The quality and accuracy of the data collected in the study and analyzed for the purpose of reporting have been assured by monitoring of the study, data management procedures, and audits. Data monitoring was conducted by PAREXEL International Clinical Monitor. Three on-site audits were performed in the United States, and 5 on-site audits at International sites.

4.5 Compliance with Good Clinical Practices

The studies used in this submission were conducted in compliance with Good Clinical Practices.

4.6 Financial Disclosures

The sponsor has provided a signed copy of FDA form 3454 certifying that clinical investigators did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator could be affected by the outcome of the study.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There were no Clinical Pharmacology studies performed specifically in association with the PONV program. However three new Phase 1 studies were submitted with this application [two drug interaction studies (PALO-03-05 and PALO-03-10) and a thorough QT/QTc study (PALO-03-11)]. PALO-03-05 was an evaluation of potential drug interaction with the NK-1 receptor antagonist aprepitant, and PALO-03-10 was an evaluation of potential drug interaction with dexamethasone.

Tolerance and dose proportionality were assessed in early Syntex studies in healthy subjects by intravenous (2092 and 0100) and oral routes (2236 and 0101) to justify dose levels used in CINV (2330 and 2332) and PONV (2500 and 2502) Phase 2 clinical trials.

Subsequent to palonosetron approval for CINV, two additional PK studies were performed in association with multiple dosing of palonosetron; a study in healthy volunteers (PALO-02-12), and a clinical efficacy and PK study in patients undergoing treatment for testicular cancer (PALO-04-09). In addition, PK simulations were performed to model several multiple dosing scenarios. These PK studies were submitted in sNDA 21-372/S006.

Medical Officer's Comments:

Aprepitant and dexamethasone are drugs that are used to prevent CINV, but would not be used for PONV, (b) (4) prevention. Nonetheless, information from these studies is useful for further characterization of the drug.

5.2 Pharmacodynamics

N/A

5.3 Exposure-Response Relationships

N/A

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication; PONV, PDNV

This application is filed in support of a single intravenous (I.V.) dose of palonosetron for the following indications: prevention of post-operative nausea and vomiting (PONV), (b) (4) (b) (4) (b) (4) for up to (b) (4)

Postoperative Nausea and Vomiting; PONV:

Postoperative nausea and vomiting is a complication of surgery experienced by 25 to 30% of surgical patients overall, and 70 to 80% of patients with multiple risk factors. Risk factors for PONV include female gender, non-smoking status, and a history of PONV or motion sickness. Other risk factors include duration of anesthesia and possibly the type of surgical procedure; gynecological, intra-abdominal laparoscopic, breast, plastic, and eye surgery being of particular high-risk. The use of inhaled volatile general anesthetics, nitrous oxide (N₂O) and administration of opioids intra and postoperatively may also increase the risk of PONV.

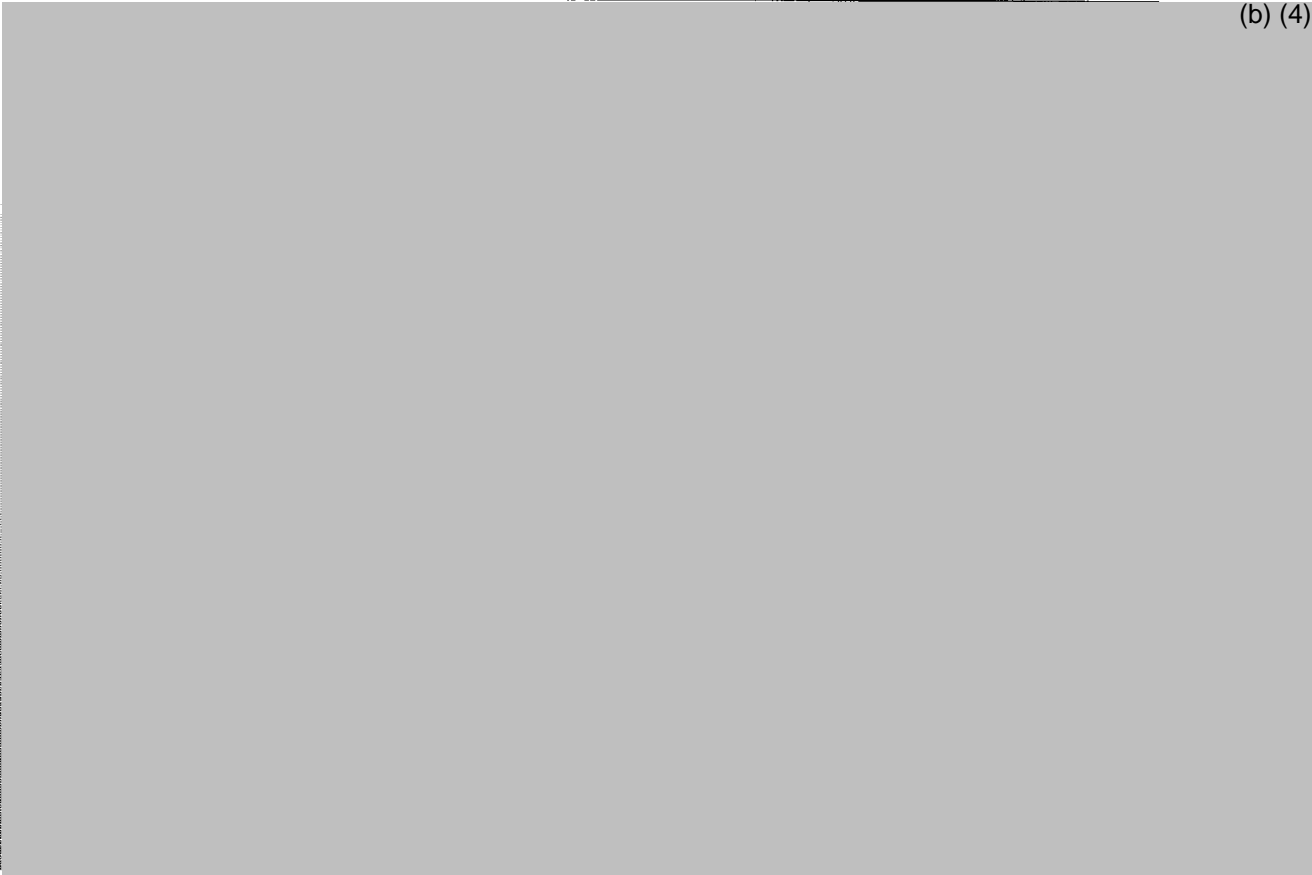
Although the neurotransmitter mechanisms that produce nausea and vomiting in the post-operative setting are not as clearly defined as those that cause chemotherapy induced nausea and vomiting (CINV), multiple aspects of the stimuli and effector mechanisms are shared by both. Neurotransmitters such as dopamine, serotonin, and substance P are involved in both emetic pathways, and drugs that interact with these neurotransmitter systems are routinely prescribed for the treatment and/or prevention of CINV and PONV.

Early PONV, defined by the sponsor as nausea and vomiting occurring from 0 to 6 hours postoperatively, typically occurs while patients are still in the PACU (post-anesthesia care unit) under observation by nursing or other healthcare staff, until such time as they are stable for discharge to the hospital ward for continued monitoring, or to home. If sent home they usually must rely on self or non-medical assistance in dealing with initial responses to delayed clinical sequelae, such as nausea and vomiting.

(b) (4)

Clinical Review
Nancy F. Snow
NDA 21-372/S-008
Palonosetron, Aloxi®

(b) (4)



Medical Officer's Comments:

The current NDA defines early PONV as nausea and vomiting occurring within 6 hours post-surgery.

(b) (4)

(b) (4)



(b) (4)



(b) (4)



(b) (4)

6.1.1 Methods

Three clinical studies provide data for the efficacy review to support the PONV (b) (4) indications being sought. These include one pivotal study (PALO-04-06) and confirmatory studies (PALO-04-07 and 2500). The two Phase 3 trials (PALO-04-06 and PALO 04-07), are double-blind, randomized investigations of palonosetron 0.025 mg, 0.050 mg or 0.075 mg given as a single I.V. bolus within 5 minutes prior to anesthesia induction, compared to placebo. The objective of these studies is to demonstrate superiority of at least one of the three palonosetron doses evaluated, versus placebo.

Medical Officer's Comments:

PALO-04-07 was originally planned as a pivotal study. However due to a flaw in execution it is submitted as a supportive study. Because of the potential unblinding of the first 130 patients, the FAS (full analysis set) are used for a sensitivity analysis of the two co-primary efficacy variables only.

6.1.2 General Discussion of Endpoints

Primary efficacy endpoints

To support the PONV (b) (4) indications the sponsor selected two co-primary endpoints; complete response (CR) at 0 to 24 hours, and CR at 24 to 72 hours, post-operatively. CR is defined as no emetic episode or use of rescue medication, and was agreed to in the December 8, 2004 review of the Special Protocol Assessment (SPA) for IND 39.797. (b) (4)
(b) (4)

In the 2003 approval of palonosetron for CINV, complete response was defined as no emetic episode and no rescue medication during the first 24 hours after administration of chemotherapy. Further, in the original granisetron NDA (NDA 20-305) a complete responder was defined as a patient with no vomiting, no more than mild nausea, no use of other anti-emetics, and not withdrawn during the specified treatment period.

The protocols for both PALO-04-06 and PALO-04-07 measured these two co-primary efficacy measures. In each study, the co-primary efficacy hypothesis was that at least one dose of palonosetron was superior to placebo in providing CR post-operatively in the 0 to 24 hour (Study 2500), and 24 to 72 hour time periods (all studies). Effectiveness in these two time intervals was tested using a closed testing procedure. The 0 to 24 hour period was tested first; if at least one comparison result was statistically significant, the 24 to 72 hour interval was tested, using the same method and the same alpha as detailed.

Medical Officer's Comments:

As demonstrated in the above examples, there has been a gradual evolution in the definition of CR from earlier studies to the present. Endpoints for the Aloxi® PONV studies submitted in this NDA were agreed to by the FDA pursuant to a SPA submitted by the sponsor.

Secondary efficacy endpoints

Secondary efficacy measures included evaluations of complete response at other time periods, and complete control (defined as complete response and no more than mild nausea) at regular intervals (2, 6, 24, 48, and 72 hours post surgery) and overall through a 72-hour post-operative observation period. Specific secondary measures are listed below.

- CR during the 0-2, 0-6, 2-6, 6-24, 24 to 48, 48 to 72, 0 to 48 and overall 0 to 72 hour time intervals
- Complete Control (CC; defined as CR, and no more than mild nausea) during the 0-2, 0-6, 2-6, 6-24, 24-48, 48-72 hours, 0-48 and 0-72 hour time intervals
- Number of patients with emetic episodes during the 0-24, 24-72, 0-2, 0-6, 2-6, 6-24, 24-48, 48-72, 0-48 and 0-72 time intervals
- Number of emetic episodes during the 0-24, 24-72, 0-2, 0-6, 2-6, 6-24, 24-48, 48-72, 0-48 and 0-72 time intervals
- Severity of nausea (4-point Likert scale) during the 0-24 hour, 24-72 hour, 0-2 hour, 0-6 hour, 2-6 hour, 6-24 hour, 24-48 hour, 48-72 hour, 0-48 hour and overall 0-72 hour time intervals.
- Time to first emetic episode
- Time to first administration and need for rescue medication
- Time to Treatment Failure (TTF – time to first emetic episode or time to first administration of rescue medication; whichever occurs first)
- Time to first fluid intake
- Time to first solid meal intake

Table 3 summarizes the primary and secondary efficacy endpoints used in the PONV trials submitted in the NDA.

(b) (4)

Table 3
NDA 21,372/S008, (b)010
(4)

Table 3.8.3.1 Efficacy Endpoints for the PONV (b)Trials (4)

Primary Efficacy Endpoint	Pivotal	Confirmatory	
	PALO-04-06	PALO-04-07	2500
Proportion of subjects with complete response (CR), which was defined as no emetic episode and no rescue medication during the first 24-hour postoperative observation period.	X	X	X
Proportion of subjects with complete response (CR), which was defined as no emetic episode and no rescue medication during the first 24-72 hour postoperative observation period.	X	X	
Secondary Efficacy Endpoints			
CR at 0-2 hours, 0-6 hours, 2-6 hours, 6-24 hours, 24-48 hours, 48-72 hours, 0-48 hours and 0-72 hours. A post-hoc analysis evaluating 6-48 and 6-72 hours was performed.	X	X	
Complete Control (defined as no emetic episodes and no nausea or mild nausea based upon verbal categoric rating) at 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 16 hours, 20 hours, and 24 hours (patients were not awakened for assessment).			X
Complete Control (defined as CR and no more than mild nausea) at 0-24 hours, 24-72 hours, 0-2 hours, 0-6 hours, 2-6 hours, 6-24 hours, 24-48 hours, 48-72 hours, 0-48 hours and 0-72 hours. A post-hoc analysis evaluating 6-48 and 6-72 hours was performed.	X	X	
Number of patients without emetic episodes during the first 4 postoperative hours.			X
Number of patients with emetic episodes at 0-24 hours, 24-72 hours, 0-2 hours, 0-6 hours, 2-6 hours, 6-24 hours, 24-48 hours, 48-72 hours, 0-48 hours and 0-72 hours. A post-hoc analysis evaluating 6-48 and 6-72 hours was performed.	X	X	
Number of emetic episodes at 0-24 hours, 24-72 hours, 0-2 hours, 0-6 hours, 2-6 hours, 6-24 hours, 24-48 hours, 48-72 hours, 0-48 hours and 0-72 hours.	X	X	
Severity of nausea (4-point Likert scale) at 0-24 hours, 24-72 hours, 0-2 hours, 0-6 hours, 2-6 hours, 6-24 hours, 24-48 hours, 48-72 hours, 0-48 hours and 0-72 hours. A post-hoc analysis evaluating 6-48 and 6-72 hours was performed.	X	X	

CR=Complete Response; VAS= Visual Analog Scale
 Source: Final Report PALO-04-06, Final Report PALO-04-07, Final Report Study 2500

Medical Officer's Comment:

CR and CC are validated endpoints that have been used in other CINV and PONV trials. Secondary endpoints may provide supportive evidence for efficacy. In PALO-04-06 the secondary efficacy endpoints of CR from 0 to 6, and 6 to 24 hours

(b) (4)

(b) (4)

(b) (4)

6.1.3 Study Design

Two Phase 3 studies, one pivotal (PALO-04-06), and one supportive (PALO-04-07), and one Phase 2 study (2500) were submitted by the sponsor in support of the PONV (b) (4) indications. These studies were conducted in patients undergoing procedures that required general anesthesia, either as inpatients or outpatients.

Both Phase 3 studies were randomized, multinational, multicenter, placebo-controlled, parallel-group, balanced, and stratified studies. All treatments were administered in a double-blind fashion. Patients received single I.V. doses of palonosetron 0.025 mg, 0.050 mg, or 0.075 mg, or placebo.

Pivotal Clinical Trial; PALO-04-06

"A Randomized, Double-blind, Multicenter, Parallel Group, Balanced, Stratified Phase 3 Study to Evaluate the Efficacy and the Safety of Single I.V. Doses of Palonosetron 0.025 mg, 0.050 mg, and 0.075 mg versus Placebo in Outpatients to Prevent Postoperative Nausea and Vomiting Following Elective Abdominal or Gynecologic Laparoscopic Surgery"

PALO-04-06 was a randomized, double-blind, multicenter, balanced, and stratified, phase 3 parallel group study to evaluate the efficacy and safety of single doses of I.V. palonosetron (0.025 mg, 0.050 mg, and 0.075 mg) versus placebo for the prevention of nausea and vomiting after surgery. The study was performed in 36 investigative centers in the United States and 7 investigative centers in Romania, between May 2005 and June 2006. Two protocol amendments were approved during the conduct of the study.

The first protocol amendment, dated 18 October 2005 modified inclusion criterion 6, which stated that the surgical procedure would last a minimum of 1 hour. The amendment allowed surgeries 20 minutes shorter than 1 hour. A second component of protocol amendment 1 related to surgical procedures that became longer or more complicated than originally expected. The protocol amendment aimed to clarify that these were not adverse events, but a result of the vagaries of surgery. The second protocol amendment, dated 06 April 2006 increased the number of centers in the US, and added centers in Romania.

Male and female outpatients, age 18 or older, at high risk of nausea and vomiting postoperatively, and scheduled for elective laparoscopic abdominal or gynecological surgery under general anesthesia, were enrolled. The inclusion criteria required at least two of the following three PONV risk factors:

- female gender
- history of PONV and/or currently prone to motion sickness
- non-smoking status

Patients were assigned to receive a single I.V. dose of palonosetron, or placebo, immediately (no more than 5 minutes) prior to induction of anesthesia (Study Day 1). Patients were randomized to treatment groups in a 1: 1: 1: 1 ratio at Visit 2 (Study Day 1). Randomization was stratified by gender, PONV history and/or currently prone to motion sickness, and smoking status. Eight strata were produced.

Three visits were scheduled: a screening visit (Days -7 to 0); a treatment visit (Day 1, the day of the surgical procedure and randomization); and a follow-up evaluation visit (Days 6 to 10). Efficacy and safety were assessed on the day of study drug administration on Day 1, and on Days

6 to 10 following surgery. Patients were contacted by telephone on Days 2, 4, and 15 to evaluate potential AEs.

Patient diaries were used to record emetic episodes, use of rescue medication, severity of nausea, severity of post-operative pain, and measures of interference with patient functioning using the modified Osoba questionnaire. Patients were asked to complete the diary each day from Day 1 to Day 3. Rescue medication for the treatment of nausea and vomiting after surgery, with the exception of palonosetron and droperidol, was permitted at the discretion of the investigator.

In PALO-04-06 three data sets were analyzed: a Full Analysis Set (FAS), a Per-Protocol (PP) set, and a safety set. The FAS was the primary analysis population for efficacy, and included patients who received study drug, anesthetic procedures and surgical operation. Patients in the FAS were assigned to the study group according to the treatment to which they were randomized.

The PP set was a subset of the FAS and was defined as all patients who completed Day 3 (i.e., the first 72 hours after T0) and were compliant with the study protocol. The safety set included all patients who received study drug and had at least one safety assessment after treatment. A secondary analysis was performed on the two co-primary efficacy variables, based on the PP set for the interval 0 to 24 hours and 24 to 72 hours.

Addendum #1 to PALO-04-06 was added to elucidate efficacy in the 6 to 48 hour and 6 to 72 hour postdischarge periods. Analyses of these two time intervals were post-hoc (non-prespecified) and performed on the PAS population.

PALO-04-07

"A Randomized, Double-blind, Multicenter, Parallel Group, Balanced, Stratified Phase 3 Study to Evaluate the Efficacy and the Safety of Single I.V. Doses of Palonosetron 0.025 mg, 0.050 mg, and 0.075 mg versus Placebo to Prevent Postoperative Nausea and Vomiting Following Elective Gynecologic or Breast Surgery"

This was a randomized, double-blind, multicenter, parallel group, balanced, stratified, placebo-controlled phase 3 study to evaluate the efficacy and safety of single I.V. doses of palonosetron (0.025 mg, 0.050 mg or 0.075 mg) versus placebo for the prevention of PONV (b) (4)

A 1-hour anticipated duration of surgery was chosen as an inclusion criterion for this study since each 30-minute increase in duration of surgery is thought to increase PONV risk by 60%. Thus a baseline risk of 10% was increased to 16% after 30 minutes.

Although several factors have been associated with an increased risk of PONV, most are only weakly associated. The factors associated with a greater risk of PONV include (1) female gender, (2) history of PONV and/or susceptibility to motion sickness, (3) non-smoking status. To evaluate patients at high risk of PONV, female patients enrolled in the study were required to have at least one of these PONV risk factors: (1) history of PONV and/or currently prone to motion sickness, (2) non-smoking status.

An increased risk of PONV (b) (4) is also associated with high-risk surgeries such as laparoscopy, laparotomy, major breast surgery, gynecological, intra-abdominal surgeries, and head and neck procedures involving the oropharynx, ears or eyes. Since the incidence of PONV is higher in females undergoing major breast or gynecological surgery, these types of surgical procedures were chosen for this study. To homogeneously balance the risk of PONV in each of the four treatment groups, randomization in the study was stratified by the following criteria: type of surgery, history of PONV and smoking status.

The sample size was estimated to be 544 patients, randomized to 1 of the 3 palonosetron groups or to the placebo group (i.e., 136 patients/group). An additional 130 patients were enrolled since the first 130 could not be used for the efficacy analyses due to a potential unblinding problem identified a few months after the start of the study. The patients originally planned, plus the additional 130 (i.e. 674 patients) were planned to be included in the safety analyses. Due to a separate potential unblinding problem identified at German centers after enrollment in the study concluded, patients from German sites were not eligible for inclusion in the primary confirmatory full analysis set. The primary confirmatory full analysis set, which excludes all potentially unblinded patients, is the set used for primary efficacy analysis.

The Full Analysis Set (FAS), Modified Full Analysis Set (MFAS), Primary Full Analysis Set (PFAS) and the Per-Protocol Set (PP) were comprised of 673, 544, 369 and 288 patients, respectively (see Table 4). The number of patients in the study was as follows; planned: 674, enrolled: 684, analyzed for safety: 673.

Table 4
Patients Analyzed in PALO-04-07

	Full analysis Set (Safety Cohort;673 patients)	Primary Full Analysis Set (369 patients)	Modified Full Analysis Set (544 patients)	Per Protocol Set (288 patients)
Placebo	168	90	136	66
Palonosetron 0.025 mg	168	88	136	69
Palonosetron 0.050 mg	169	96	137	79
Palonosetron 0.075 mg	168	95	135	74

Dose Selection for Phase 3 (Studies 2500, 2502)

The fixed doses selected for Phase 3 PONV studies were based on results of the Phase 2 dose-ranging studies 2500 and 2502. In study 2500, a single I.V. dose of palonosetron was administered to women undergoing vaginal or abdominal hysterectomies at one of five dose levels (0.1 µg/kg, 0.3 µg/kg, 1µg/kg, 3 µg/kg or 30 µg/kg), or placebo. In study 2502, surgical patients were treated with a single oral dose of palonosetron at one of five dose levels (0.3µg/kg, 1 µg/kg, 3µg/kg, 10 µg/kg or 30 µg/kg) or placebo.

In study 2500, patients receiving palonosetron doses of 1 µg/kg and 30 µg/kg had a favorable clinical response compared to placebo. Similar benefits were found for the 1 µg/kg (CR = 58%, p=0.013), 10 µg/kg (CR = 59%, p=0.009) and 30 µg/kg (CR = 53%, p=0.018) doses in Study 2502. There appeared to be an efficacy plateau starting at the 1 µg/kg dose level after both I.V. and PO dosing. Table 5 shows therapeutic benefit compared to placebo for the 1 µg/kg and 30 µg/kg doses in Study 2500; all other comparisons, p=NS.

Table 5
Study 2500
Complete Response Rates

Evaluation Time (hr)	Placebo	0.1 µg/kg 0.0075 mg	0.3 µg/kg (0.025mg)	1 µg/kg 0.075 mg	3 µg/kg 0.25 mg	30 µg/kg 2.25 mg
0 to 24 hours	12 (19%)	16 (34%)	23 (34%)	27 (44%)	20 (30%)	30 (45%)
Prevention gain		15%	15%	25%, p0.004	11%	26%, p 0.002

Taking both studies into consideration, 0.3 µg/kg and 1 µg/kg, were selected for Phase 3 clinical development. At these dosages, approximately 3 and 10-fold lower, respectively, than doses approved for the CINV indication, palonosetron was known to be well-tolerated. For convenience of use, the two weight-based doses were converted to fixed doses by multiplying with a value of 70 kg (average body weight) and further rounded up to the fixed palonosetron doses of 0.025 mg and 0.075 mg. An intermediate dose of 0.050 mg was also evaluated, to determine if it might be fully effective.

Medical Officer's Comment:

Studies 2500 and 2502 provided rationale for the choice of doses of palonosetron used in the two Phase 3 studies, as well as support for the efficacy findings in PALO-04-06.

6.1.4 Efficacy Findings

As discussed under the general discussion of endpoints, there were two co-primary endpoints specified in the Phase 3 protocols; complete response from 0 to 24 hours, and complete response from 24 to 72 hours.

In PALO-04-06 the number of patients with no nausea or need for rescue medications (i.e., CR) in the 0 to 24 hour time interval, was highest in the palonosetron 0.050 mg and 0.075 mg groups (39.4% and 42.8%, respectively) and lowest in the placebo group (25.9%). The differences between palonosetron and placebo were 7.2%, 13.5% and 16.8%, for the 0.025 mg, 0.050 mg and 0.075 mg doses, and provide support for the effectiveness of the intermediate and high dose levels. However, in this study a clinically meaningful and statistically significant difference between palonosetron and placebo was not seen in the 24 to 72 hour postoperative observation period, the second co-primary endpoint.

A lack of differentiation between palonosetron and placebo response rates in the 24 to 72 hour period may have been due to the fact that after 24 hours fewer patients in either group (palonosetron or placebo) experienced emesis.

For example, between 24 and 72 hours only 8.9% of patients in the placebo group complained of emesis, and only 8.7% of patients in the 0.075 mg palonosetron had emesis. (b) (4)

(b) (4) This situation is contrasted with the 0 to 24 hours time frame wherein 44.4% of patients taking placebo had emetic episodes, compared with 33.3% of patients taking 0.075 mg of palonosetron. In other words, the closer in time to the surgery, the more likely one is to experience emesis, and derive benefit from the drug.

Safety and efficacy were evaluated at multiple time intervals during the study. At discharge patients were given diaries to record symptoms, and also contacted by telephone. As Table 6 shows, a benefit over placebo was seen during the 0 to 6 hour time period for the 0.075 mg dose and during the 0 to 24 hour time period for the 0.050 mg and 0.075 mg doses (as discussed above). Evaluation of patients during the 6 to 24 hour period demonstrated a significant clinical benefit from palonosetron at the 0.075 mg dose level. These same benefits were not seen at lower doses in this time frame.

Table 6
COMPLETE RESPONSE RATES
PALO 04-06

Evaluation Time (hr)	Placebo	Palonosetron Doses		
		0.025	0.050	0.075
0 to 6 hours Prevention gain	37%	41.2% 4%, NS	46% 9%, NS	49.3% 12%, p 0.0415
0 to 24 hours Prevention gain	25.9%	33.1% 7.2%, NS	39.4% 13.5%, p 0.0171	42.8% 16.8%, p 0.0035
6 to 24 hours Prevention gain	36.3%	39% 2.7%, NS	42.3% 6%, NS	48.6% 12.3%, p 0.038

Although results from PALO-04-07 were not included in the efficacy analysis of PONV (b) (4) the FAS was used for a sensitivity analysis of the two co-primary efficacy variables. Differences from placebo for palonosetron 0.025 mg, 0.050 mg, and 0.075 mg for CR in the 0 to 24 hour period were 13.1% (p=0.0129), 14% (p=0.0091), and 19.7% (p=0.00002). The following Table 7 shows that there was a prevention gain over placebo for all doses from 0 to 24 hours, and for the 0.075 mg dose for the 24 to 72 hour time period. The latter results were not replicated in pivotal study PALO-04-06.

Table 7
Sensitivity Analysis FAS; PALO-04-07
Complete response rates PALO-04-06

Evaluation Time (hr)	Placebo	0.025 mg	0.050 mg	0.075 mg
0 to 24 hours Prevention gain	32.1%	45.2% 13.1%, p 0.0129	46.2% 14.1%, p 0.0091	51.8% 19.7%, p 0.0002
24 to 72 hours Prevention gain	48.8%	54.8% 6%, NS	59.2% 10.4%, NS	66.7% 17.9%, p 0.0008

Medical Officer's Comments:

In the PALO-04-07 sensitivity analysis, differences from placebo for palonosetron 0.025 mg, 0.050 mg, and 0.075 mg for complete response in the 0 to 24 hour period were 13.1% (p=0.0129), 14% (p=0.0091), and 19.6% (p=0.00002). These data lend support to the results of PALO-04-06. Table 7 shows that there was a prevention gain over placebo for all doses from 0 to 24 hours, and for the 0.075 mg dose for the 24 to 72 hour time period. The latter results were not replicated in pivotal study PALO-04-06.

Thus for the primary efficacy parameter of CR in the 0 to 24 hour post-operative period, in pivotal study PALO-04-06, and confirmatory study 2500, the 0.075 mg dose consistently separated from placebo. No other dose was so distinguished, and these dose response data support the selection of 0.075 mg as the proposed market dose.

Study 2500

Unlike the Phase 3 studies, study 2500 included only one primary efficacy endpoint, CR from 0 to 24 hours. Approximately 185 patients had been enrolled in the study when a review of blinded patient response data revealed a lower-than-anticipated overall number of patients experiencing complete response. The protocol was amended to delete the 0.1 µg/kg palonosetron group and add a 30 µg/kg palonosetron group to the study. According to the sponsor, this provided an opportunity to fully define the antiemetic dose-response curve for palonosetron, and to reduce the number of patients receiving potentially ineffective doses. Data obtained from the deleted dose group were listed and summarized, but not analyzed statistically. The total number of doses in analysis, and the conduct of the study remained unchanged. At completion of the study, 381 patients had been enrolled.

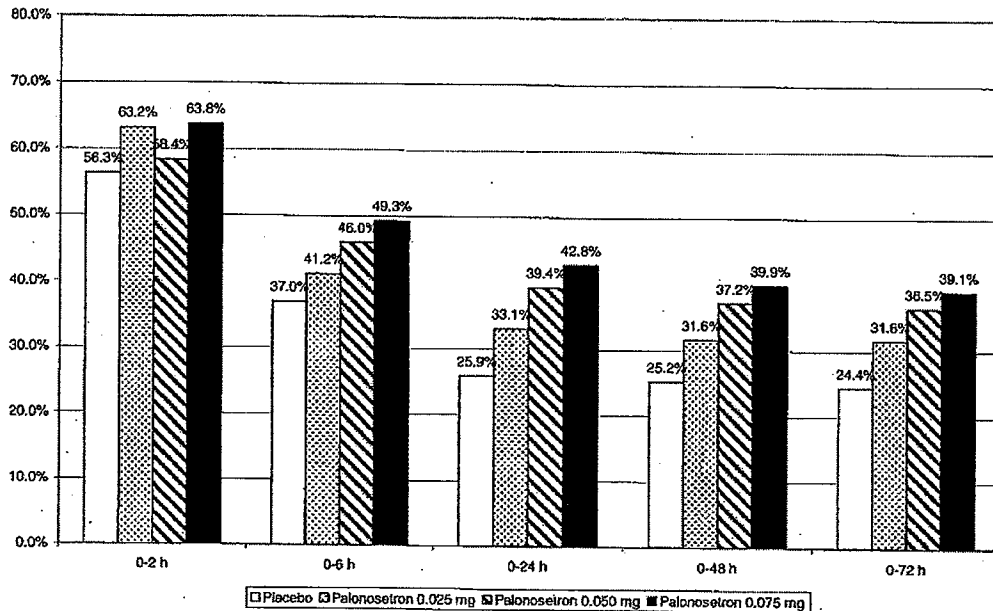
The proportion of patients with complete response (0 to 24 hours) showed a gain for the 1 µg/kg and 30 µg/kg dose groups compared to placebo. Weight based doses were converted to fixed doses by multiplying with a value of 70 kg (average body weight) and further rounded up to the fixed palonosetron doses of 0.025 mg and 0.075 mg. Table 5 of this review shows a greater efficacy response from palonosetron than placebo in Study 2500.

CR 0 to 48, 0 to 72 hours

The studies also looked at subjects with CR at further time periods. In both the 0 to 48 hour and 0 to 72 hour periods the CR rate for the 0.075 mg group exceeded that of placebo by 14.7% (p=0.0100) and 14.7% (p=0.0096). Results from supportive study PALO-04-07 (MFAS) were similar. In both studies, CR rates for the 0.075 mg dose over the 0 to 48 and 0 to 72 hour periods post-operatively, (b) (4) were statistically separated from placebo.

However, these finding cannot override the lack of significant clinical response in the 24 to 48, and 24 to 72 hour time periods. During these periods placebo response was high, and palonosetron response rates were not significantly distinguished from placebo. Figure 2, with data from PALO-04-06, illustrates these findings, and shows a clear dose response for the time intervals 0 to 6, 0 to 24, 0 to 48 and 0 and 72 hours. Absent from Figure 2 are complete response rates for 24 to 72 hours.

Figure 2: Complete Response: Analysis over Time



Source: Section 16.5, Table 3.3.1

Medical Officer's Comment:

Data presented in Tables 6 and 7 of this review show success in meeting the co-primary endpoint of CR 0 to 24 hours for two dose levels of palonosetron (0.075 and 0.050 mg), but not the co-primary endpoint of CR 24 to 72.

Although not used as a pivotal study, a sensitivity analysis of the FAS for PALO-04-07 showed a benefit over placebo for all doses from 0 to 24 hours. In the 24 to 72 hours period only the 0.075mg dose showed clinical benefit over placebo. Data from both studies support the PONV

(b) (4) indications for 0 to 24, and 6 to 24 hours (b) (4)

Secondary Endpoints:

Secondary endpoints analyzed CR rates at further time periods. (b) (4)

(b) (4) The proportion of patients with CR during the 0-2, 0-6, 2-6, 6-24, 24-48, 48-72 hour time frames, as well as during the overall 0-48 and 0-72 hours postoperative observation periods, were evaluated as additional parameters for the characterization of the antiemetic effect of the study drug.

For the longer time intervals, a dose response was seen, with the greatest proportion of patients with CR occurring in the palonosetron 0.075 mg group.

Results of logistic regression analysis showed that the 0.075 mg palonosetron group had a statistically significant different proportion of patients with CR compared to placebo for the 0-6 hours ($p=0.0415$), and 6-24 hours ($p=0.0384$) time intervals. At these time points, the difference in the proportion of patients with CR favored palonosetron 0.075 mg (12.2% and 12.3%, respectively). For the longer 0-48 hour and 0-72 hour time intervals, the proportion of patients with CR in the palonosetron 0.075 mg group was also significantly higher than the proportion of patients with CR in the placebo group ($p=0.0100$ and 0.0096 , respectively).

A statistically significant difference between palonosetron 0.050 mg and placebo was also achieved during the overall time periods 0-48 hours ($p=0.0313$) and 0-72 hours ($p=0.0303$). Logistic regression analysis did not show any statistically significant difference in the proportion of patients with CR for the comparison of palonosetron 0.025 mg and placebo, and for any dose of palonosetron over any other dose ($p>0.05$).

Medical Officer's Comment:

Figure 2 (above) taken from study PALO-04-06 shows a clear dose response for the secondary endpoints of 0 to 6h, 0 to 48h, and 0 to 72h, and the primary endpoint of 0 to 24h.

6.1.5 Clinical Microbiology

N/A

6.1.6 Efficacy Conclusions

The sponsor has applied for two indications, PONV (b) (4)
(b) (4) In pivotal study PALO-04-06, for the 0 to 24 hour time period, comparisons of palonosetron with placebo showed that patients did not experience as much vomiting or require use of rescue medication when given 0.050 mg (prevention gain 13.5%, $p=0.0171$) or 0.075 mg (prevention gain 16.8%, $p=0.0035$) of palonosetron, compared to 0.025 mg of palonosetron or placebo.

These clinically meaningful results suggest that patients who receive one dose of palonosetron prior to surgery will continue to accrue benefits from the drug throughout the first 24 hours. During the first 6 hours post-operatively, a significant number of patients will remain free of an untoward sequelae of surgery, nausea and vomiting. Similarly, patients discharged will continue to be protected, and not require further treatment for nausea and vomiting.

The same was not the case for the time interval 24 to 72 hours (co-primary endpoint). During this period a distinction between placebo and palonosetron was less evident, and all p-values exceeded the pre-set adjusted significance levels. Thus palonosetron treatment did not surpass placebo in the treatment of either PONV (b) (4) during this later time frame.

For the longer 0 to 48 hour and 0 to 72 hour periods, the proportion of patients with clinical benefit in the palonosetron 0.075 mg group was higher than that in the placebo group (0-48 hr:

Placebo 25.2%, Palo 0.075 mg 39.9%; 0-72 hr Placebo: 24.4%, Palo 39.1%). (b) (4)
(b) (4)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Because palonosetron has been marketed in the United States since July 2003, safety data from previous clinical studies and post-marketing experience are widely available.

The variables used to assess the safety of single doses of palonosetron for the prevention of PONV (b) (4) include physical examination, vital sign measurements, 12-lead electrocardiogram (ECG) evaluations, clinical laboratory tests, and evaluation of adverse events. The palonosetron PONV (b) (4) safety database is comprised of safety data from 1952 subjects enrolled in four palonosetron PONV (b) (4) clinical trials, in which 1520 received palonosetron. In addition to safety information from pivotal and supporting studies, safety data on the effects of palonosetron on cardiac conduction (QTc) was submitted in thorough QT study PALO-03-11.

In *PALO-04-06* the safety cohort consisted of 547 patients evenly divided between three palonosetron doses, and placebo (Table 8). Two-hundred sixty-six (266/547; 48.6%) patients experienced at least one treatment emergent adverse event (TEAE). The number of TEAEs was higher in the palonosetron 0.025 mg (52.2%) and 0.050 mg (50%) groups, and placebo (48.9%), compared to the 0.075 mg palonosetron group (43.3%). The most common TEAEs were headache, abdominal pain, post-procedural pain, constipation, and flatulence.

As noted in Table 9 below, the largest number of serious adverse events (SAEs) was seen in the lowest palonosetron dose, 0.025 mg. No deaths occurred in any cohort.

Table 8
PALO-04-06
Overview of All Adverse Events (Safety Set, N=547)

	Placebo N=137			0.025 mg N=136			0.050 mg N=138			0.075 mg N=136			Total N=547		
	n	%	n*	n	%	n*	n	%	n*	n	%	n*	n	%	n*
AE	4	2.9	5	2	1.5	2	3	2.2	3	1	0.7	1	10	1.8	11
Pre-treatment AE															
Any TEAEs	67	49	131	71	52	141	69	50	143	59	44	128	266	49	543
Severe TEAE	6	4.4	6	4.4	6	6	4	2.9	6	5	3.7	5	21	3.8	23
SAEs	4	5.1	5	7	5.1	8	2	1.4	2	4	2.9	5	17	3.1	20
Drug-related TEAE	13	8.8	15	12	8.8	15	15	11	22	9	6.6	11	49	9	63
Drug-related SAE	1	0	1	0	0	0	0	0	0	0	0	0	1	0.2	1
TEAE causing withdrawal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

n=number of patients with events; n*=number of events; %=percentage of patients with events

In **PALO-04-07** 45 SAEs occurred in 27 patients, and 51 serious TEAEs were seen in 37 patients. These events were dispersed among placebo and palonosetron groups. There were no deaths or TEAEs resulting in withdrawal from the study.

Table 9
PALO-04-07
Serious AEs

	Placebo	Palonosetron 0.025 mg	Palonosetron 0.050 mg	Palonosetron 0.075 mg	Total
	n (%) n*	n (%) n*	n (%) n*	n (%) n*	n (%) n*
Serious TEAEs	9 (5.4) 16	11 (6.5) 15	11 (6.5) 13	6 (3.6) 7	37 (5.5) 51
SAEs	8 (4.8) 16	10 (6.0) 18	5 (3.0) 5	4 (2.4) 6	27 (4) 45
Drug-related serious TEAEs	-0-	4 (2.4) 7	-0-	-0-	4 (0.6) 7

n=number of patients with AEs, n* = number of AEs

The safety analysis of **Study 2500**, which was conducted on 381 enrolled patients, showed that palonosetron was well tolerated at all dose levels. Most of the 502 adverse events reported during the study were mild or moderate (97.6%); 3.6% were probably/possibly related to study medication. The most frequently reported AEs in palonosetron treated subjects were constipation, headache, pruritis, insomnia and fever. Twelve-lead ECGs performed three to seven days postoperatively had many nonsignificant findings, but no differences between palonosetron treated groups and placebo. There were no prolongations of PR, QRS, QTc, and QT intervals.

Medical Officer's Comments:

Overall, the safety evaluation of PALO 04-06 indicates no significant differences between placebo and palonosetron groups, or among palonosetron groups. All doses of I.V. palonosetron were well tolerated.

7.1.1 Deaths

Two patients died in Phase 2 trials. In study 2500 a patient died from a pulmonary embolism, and in study 2501 a patient died from ovarian cancer. Neither death appeared related to palonosetron. No patients died in Phase 3 trials

7.1.2 Other Serious Adverse Events

Serious adverse events (SAEs) were collected over the 30 days following dosing, and were defined as events which results in death; were life-threatening; required subject hospitalization or prolonged existing hospitalization; resulted in persistent or significant disability or incapacity; or were congenital anomalies or birth defects. SAEs also included other medical events that were thought to jeopardize the subject or require medical or surgical intervention.

In study **PALO-04-06**, 17 patients experienced 20 SAEs (14 patients experienced 1 SAE, 3 patients had 2 SAEs each). Of these 20 SAEs, 5 were observed in both the palonosetron 0.075 mg and placebo groups, 8 in the palonosetron 0.025 mg group, and 2 in the 0.050 mg group.

None of the SAEs appeared related to study medication. Two involving the cardiovascular system occurred in the placebo arm and are described below.

- Patient 60067; 77 year old female in placebo arm experienced bradycardia and syncope 27 days after receiving study drug. The patient suffered 2 episodes of syncope with loss of balance, and struck her head when falling. CT and MRI (-) for acute event. Patient underwent pacemaker placement, and recovered, with sequelae from syncope and bradycardia. The investigator judged the bradycardia to be moderate in intensity and syncope to be severe in intensity, and both diagnoses unrelated to study medication.
- Patient 60357; 51 year old female in placebo group experienced clinically significant QTc interval prolongation 15 minutes after receiving study drug. Three baseline electrocardiograms revealed normal sinus rhythm (with a QTcB of 440, 435 and 431). An ECG 15 minutes post-treatment, revealed a sinus rhythm with sinus arrhythmia and a QTcB of 515. The QTc returned to a baseline of 449, 3 to 6 hours post-treatment. During the pre-, intra-, and post-surgery phases the patient was administered the following drugs for anesthesia: fentanyl, propofol, mivacurium chloride, midazolam, nitrous oxide, lidocaine, sevoflurane, glycopyrronium bromide. Pain management post-surgery included pethidine hydrochloride, morphine and propacet (paracetamol plus dextropropoxyphene napsilate). Sponsor could not exclude relationship between study drug and AE. However concomitant mediations may have played a role.

A complete list of these events is available in sponsor's Table 60.

Table 60: Serious Treatment-Emergent Adverse Events (Safety Set, N=547)

System Organ Class Preferred Term (MedDRA, v 8.0)	Patient number	Placebo/Dose Palonosetron	Relationship	Intensity	Recovered
Blood and lymphatic system disorders:					
Neutropenia	60246	0.025 mg	not related	moderate	Yes
Cardiac disorders:					
Bradycardia	60067	Placebo	not related	moderate	Yes*
Gastrointestinal disorders:					
Abdominal pain	60179	0.075 mg	not related	severe	Yes
Abdominal pain	60447	0.025 mg	unlikely	moderate	Yes
Ileus paralytic	60603	0.025 mg	unlikely	severe	Yes
Intestinal perforation	60103	0.025 mg	not related	mild	Yes
Pancreatitis acute	60473	0.075 mg	unlikely	severe	Yes
Infections and infestations:					
Lobar pneumonia	60037	0.075 mg	not related	mild	Yes
Injury, poisoning and procedural complications:					
Post procedural bile leak	60037	0.075 mg	not related	mild	Yes
Post procedural pain	60034	0.050 mg	not related	moderate	Yes
Post procedural pain	60035	0.025 mg	not related	severe	Yes
Post procedural pain	60318	Placebo	not related	severe	Yes
Urinary bladder rupture	60411	0.050 mg	unlikely	severe	Yes
Investigations:					
Electrocardiogram QT corrected interval prolonged	60357	Placebo	possible	mild	Yes
Nervous system disorders:					
Syncope	60067	Placebo	not related	severe	Yes*
Renal and urinary disorders:					
Dysuria	60634	Placebo	not related	severe	Yes
Urinary retention	60452	0.025 mg	unlikely	moderate	Yes
Reproductive system and breast disorders:					
Pelvic pain	60008	0.025 mg	not related	moderate	Yes
Surgical and medical procedures:					
Pain management	60103	0.025 mg	not related	mild	Yes
Vascular disorders:					
Hypertension	60544	0.075 mg	not related	moderate	Yes

Source: Section 16, Listing 16.2.7.5

MedDRA=Medical Dictionary for Regulatory Activities

Patients are identified by randomization number

*=patient recovered with sequelae

PALO-04-07

A total of 45 serious TEAEs occurred in 27 patients: 8 patients (4.8%) in the placebo group, and 10 patients (6.0%), 5 patients (3.0%), and 4 patients (2.4%) in the palonosetron 0.025 mg, 0.050 mg and 0.075 mg groups, respectively. Seven of the 45 were possibly treatment-related.

Because palonosetron (and all 5HT₃ antagonists) has been associated with QTc prolongation particular attention was paid to cardiac-related events. Table 10 shows serious treatment emergent adverse events of the cardiovascular system. One of the 4, patient #73139, experienced QTc prolongation.

Table 10
Cardiac-related TEAEs
PALO-04-07

Patient 73160	0.025 mg	weakness, abnormal ECG (cardiac enzymes (-), hypokalemia)	possibly related
Patient 72491	0.025 mg	intra-operative bradycardia 2 degree AV block	possibly related
Patient 72805	0.025 mg	atrial fibrillation x 2, non-specific t-wave abnormality	possibly related
Patient 73139	0.025 mg	intra-operative bradycardia, QTc of 483	possibly related

Patient #73139 was a 65-year old female scheduled for elective gynecological surgery due to vulvar cancer (also with a history of diabetes). Fifteen minutes after study medication administration she developed bradycardia. A change from baseline QT value of 412 to 490 msec was observed. These events were followed by bradycardia and mild hypotension requiring a dopamine infusion. The patient recovered from the events. According to the study report, the investigator assessed the event of bradycardia as life threatening, severe in intensity, and possibly related to the study medication. The events of hypertension and QT prolongation were initially judged as serious adverse events; later they were downgraded to non-serious adverse events. The sponsor agreed.

Medical Officer's Comment:

The episodes of bradycardia and cardiac conduction abnormalities occurred intra-operatively, when patients received anesthetic agents and palonosetron. It is difficult to determine causality since both drugs could potentially affect the QT interval. Both patients recovered the CVAE.

7.1.3 Dropouts and Other Significant Adverse Events

No patients were discontinued from either Phase 3 study due to SAEs. One subject in Phase 2 study 2500 died of a pulmonary embolism. She received > 0.075 mg of palonosetron.

7.1.3.1 Overall profile of dropouts

N/A

7.1.3.2 Adverse events associated with dropouts

N/A

7.1.3.3 Other significant adverse events

N/A.

7.1.4 Other Search Strategies

N/A

7.1.5 Common Adverse Events

As noted, in PALO-04-06 266 out of 547 patients (48.6%) experienced at least one TEAE. The incidence of TEAEs was similar between the placebo (48.9%) and palonosetron groups (43.4 to 52.2%), and no dose-related effect on the incidence of TEAEs was observed. Table 11 shows the most common TEAEs.

Table 11
 PALO-04-06
 Overview of Most Common TEAEs

	Placebo (n=137) n (%) n*	Palonosetron 0.025 mg (n=136) n (%) n*	Palonosetron 0.050 mg (n=138) n (%) n*	Palonosetron 0.075 mg (n=136) n (%) n*
All TEAS	67 (48.9) 131	71 (52.2) 141	69 (50) 143	59 (43.4) 128
Headache	16 (11.7) 17	18 (13.2) 18	21 (15.2) 24	14 (10.3) 16
Abdominal Pain	8 (5.8) 10	9 (6.6) 13	12 (8.7) 15	9 (6.6) 11
Constipation	6 (4.4) 6	8 (5.9) 8	14 (10.1) 14	10 (7.4) 10
Flatulence	4 (2.9) 4	6 (4.4) 6	7 (5.1) 9	4 (2.9) 6
Post procedural pain	8 (5.8) 12	8 (5.9) 14	4 (2.9) 4	5 (3.7) 7

In PALO-04-07 gastrointestinal disorders, injury, poisoning, procedural complications and psychiatric disorders were most frequently reported, with an incidence of >2% in all treatment groups. GI disorders were reported with the greatest frequency in the palonosetron 0.050 mg group (37.3%), compared to placebo (27.4%) and palonosetron 0.025 mg and 0.075 mg patients (27.4% and 28% respectively).

7.1.5.1 Eliciting adverse events data in the development program

On Day 1 (Visit 2), patients were monitored for the occurrence of AEs by a member of the clinical staff during the administration of the study drug and anesthetic agents, and until discharged. At each subsequent telephone contact and at the final visit, patients were questioned about the occurrence of new AEs and about the outcome of any AEs recorded previously.

After the surgical procedure patients were observed in a post-anesthesia unit until ready for discharge to home, or admitted to the inpatient facility for further treatment. In this controlled

environment eliciting of adverse events was a component of post-operative monitoring. Once discharged home, patients were contacted by telephone by a member of the study staff on study days 2 and 4 to assess safety. Details of the call are recorded in the CRF.

Patients returned to the study site for a visit with the investigator between Days 6-10 for physical exam, and laboratory assessments. On study day 15 patients were again contacted by telephone to inquire about new or ongoing AEs, or changes in concomitant medications since the last visit to the study site.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The terms used to describe adverse events in the MedDRA dictionary, compared to terms used by patients and investigators, were generally similar. For example, the most common AEs, headache and constipation, were classified the same by both groups. Since the study drug was administered only once, the number of AEs was relatively low.

7.1.5.3 Incidence of common adverse events

The most common adverse events related to study drug administration occurred in the nervous and gastrointestinal systems in the form of headache and constipation. Within palonosetron treatment groups (Phase 2 and 3 studies), the incidence of headache ranged from 2% at the <0.025 mg dose to 11 % at the > 0.75 mg dose, while placebo incidence was 4%. The incidence of constipation ranged from 2% in the 0.075 mg dose group to 11 % in the < 0.025 mg dose group (which also had the lowest sample size (n=47)); placebo incidence was 3%. Table 12 (section 3.1.3) shows these data.

7.1.5.4 Common adverse event tables

The following adverse events were seen in ≥1% of patients receiving palonosetron in study 2500, PALO-04-06 and PALO-04-07. Data are given for the 0.075 mg dose, the to-be-marketed dose, compared to placebo.

Table 12
Patients reporting AEs probably/possibly related to Study Drugs (≥1% Subjects)

Event	Palonosetron 0.075 mg	Placebo
Any AE	66 (20%)	76 (21%)
No AE	270 (80%)	293 (79%)
Bradycardia	13 (4%)	16 (4%)
Sinus bradycardia	3 (1%)	0
Tachycardia	2 (1%)	1 (<1%)
Constipation	8 (2%)	11 (3%)
Flatulence	3 (1%)	4 (1%)
ECG QT prolonged	16 (5%)	11 (3%)
AST/ALT increased	2 (1%)	3 (1%)
Headache	11 (3%)	14 (4%)
Urinary retention	2 (1%)	1 (<1%)
Pruritis	3 (1%)	3 (1%)

Medical Officer's Comments:

As Table 12 shows, the incidence of AEs in the palonosetron and placebo groups was similar. QT prolongation is seen in both groups, although slightly more with palonosetron. Drugs used peri- and intra-operatively may also have affected the QT interval.

7.1.5.5 Identifying common and drug-related adverse events

No clear dose-response was seen in the palonosetron studies reviewed for this NDA. For example the common AE of constipation was seen in 7.4% of the 0.075 mg patients, compared to 10.1% among those in the 0.050 mg group. Similarly, abdominal pain was reported in 8.7% of patients receiving 0.050 mg of palonosetron, 5.8% in the placebo group, and 6.6% in the 0.025 mg and 0.075 mg groups. A higher percentage of patients developed flatulence in the palonosetron 0.050 mg group (5.1 %) compared with the palonosetron 0.025 mg group (4.4%), and the placebo and palonosetron 0.075 mg groups (both 2.9%). The most frequently reported nervous system disorder, headache, was again reported more frequently in the 0.050 mg dose (10.3%) patients compared to 15.2% in the 0.050 mg palonosetron group.

7.1.5.6 Additional analyses and explorations

N/A

7.1.6 Less Common Adverse Events

N/A

7.1.7 Laboratory Findings

Although isolated instances of laboratory abnormalities were seen in studies submitted for this NDA, no trends or consistent patterns were seen. For both Phase 3 studies (P ALO-04-06, PALO-04-07) the blood samples for routine laboratory evaluations were taken at screening and at final study visit Study Day 6-10. All samples of each study were sent to a central laboratory for the analytical determinations.

Laboratory values are contained in dataset ADLB.xpt for each study. Values are entered for each visit during which they were done.

7.1.7.1 Overview of laboratory testing in the development program

Clinical laboratory data were assessed for hematology, serum chemistry and urinalysis. Blood and urine samples for routine hematology and chemistry evaluations and urinalysis were drawn at screening and at the final visit, Visit 3 (Day 6 to 10). In each treatment group, the majority of patients had normal hematologic values at both baseline (Visit 1) and Visit 3.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory values were obtained for all studies submitted with this NDA. Because the study drug was administered only once, limited controlled comparisons are available, and no signal of an effect of palonosetron was observed.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 *Analyses focused on measures of central tendency*

N/A

7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

N/A

7.1.7.3.3 *Marked outliers and dropouts for laboratory abnormalities*

N/A

7.1.7.4 Additional analyses and explorations

N/A

7.1.7.5 Special assessments

N/A

7.1.8 Vital Signs

Vital sign measurements, including heart rate, blood pressure and body temperature, were recorded at screening, Day 1 approximately 15 minutes post study drug administration, and on study Visit 3 (Day 6 to 10).

7.1.8.1 Overview of vital signs testing in the development program

Baseline systolic and diastolic blood pressure values were similar for patients across treatment groups. Systolic and diastolic blood pressure decreased from baseline to Visit 2, at 15 minutes post-dose, in all treatment groups and the mean changes in blood pressure from baseline to Visit 2 were similar among all four treatment groups, with no notable differences between groups. There was no relevant change from mean baseline to Visit 3 (Study days 6 to 10) in all treatment groups. There was a large variation among individual patients within groups (as shown by the large standard deviations).

Baseline (Visit 1) heart rate values were similar for patients across treatment groups. No relevant changes for mean heart rate from baseline (Visit 1) to Visits 2 and 3 were observed. Again, there was a large variation among individual patients within groups (as shown by the large SDs).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

N/A

7.1.8.3 Standard analyses and explorations of vital signs data

N/A

7.1.8.3.1 *Analyses focused on measures of central tendencies*

N/A

7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

N/A

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

N/A

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The effects of palonosetron on cardiac conduction were explored in preclinical studies, Phase 2 study 2500, Phase 3 trials, PALO-04-06 and PALO-04-07, and thorough QT/QTc study PALO-03-11.

As the sponsor notes in the NDA submission, Palonosetron inhibited hERG and hHNa channels stably expressed in HEK293 cells in a concentration dependent manner in animal studies. The IC50 values were 1.9-2.04 μ M and 6.5 μ M for hERG and hHNa channels, respectively. In dog Purkinje fibers, Palonosetron induced a dose dependent increase in action potential duration (APD70 and APD90) at 0.3 μ M and 3.0 μ M, under normal (60 ppm) and - to a larger extent - under low (12 ppm) stimulation rates, suggesting a reverse use dependency. In conscious dogs administered Palonosetron by the intravenous route and monitored via telemetry for 24 hours (10 and 100 μ g/kg) or 72 hours (1000 μ g/kg), there were no pharmacologically relevant effects on arterial blood pressures, heart rate, PR interval, QRS complex duration, QT interval, QTc and in the frequency and occurrence of atrioventricular blocks.

Medical Officer's Comments:

Since Palonosetron is already approved for CINV, a complete PharTox review is contained in the original NDA review, and discusses in detail these animal findings.

PALO-04-06

A 12-lead ECG was performed for all patients at Screening (Visit 1), and at Visit 2 (day of study drug administration) 15 minutes post study drug administration and within 3 to 6 hours post study drug administration.

As seen in sponsor's Table 70, changes in QTc from screening to 15 minutes and 3 to 4 hours post-dose did not differ significantly between placebo and palonosetron treated patients.

Table 70: Changes for QTc at Visits 1 and 2 (Safety Set, N=547)

Changes from:	Placebo (N=137)	Palonosetron 0.025 mg (N=136)	Palonosetron 0.050 mg (N=138)	Palonosetron 0.075 mg (N=136)
	n (%)	n (%)	n (%)	n (%)
Visit 1^a to Visit 2^b (15 min)				
Patients with Values	101	99	110	98
QTc by Bazett [msec]				
30 to 60 msec	48 (35.0)	39 (28.7)	46 (33.3)	43 (31.6)
>60 msec	12 (8.8)	8 (5.9)	6 (4.3)	7 (5.1)
QTc by Fridericia [msec]				
30 to 60 msec	36 (26.3)	26 (19.1)	26 (18.8)	24 (17.6)
>60 msec	3 (2.2)	1 (0.7)	1 (0.7)	4 (2.9)
Visit 1^a to Visit 2^b (6h)				
Patients with Values	121	123	123	119
QTc by Bazett [msec]				
30 to 60 msec	31 (22.6)	35 (23.7)	25 (18.1)	32 (23.5)
>60 msec	3 (2.2)	2 (1.5)	4 (2.9)	1 (0.7)
QTc by Fridericia [msec]				
30 to 60 msec	24 (17.5)	18 (13.2)	20 (14.5)	22 (16.2)
>60 msec	3 (2.2)	1 (0.7)	1 (0.7)	1 (0.7)

Source: Section 16.5, Tables 6.3.3.2 and 6.3.4.2

N= number of patients in each treatment group; n= number of patients in each category; a=Screening; b=Day of study drug administration; Electrocardiogram recorded at 15 minutes postdose and 3-6 hours, prior to discharge; percentages are based on the total number of patients in each treatment group.

PALO-04-07

A 12-lead ECG was performed for all patients at Visit 1 (baseline) and at Visit 2 (day of study drug administration), 15 minutes and approximately 6 hours post study drug administration.

At baseline visit the majority of patients had normal ECG recordings. The mean QT intervals ranged from 380.9 msec (placebo) to 385.9 msec (0.075mg). The mean QT and QTc intervals at 15 minutes post study drug administration showed a marked increase compared to baseline. The QTc prolongation was consistent throughout all treatment groups. The mean tendency analysis showed evidence of a QT interval prolongation at 15 min post drug administration with a subsequent tendency to normalize after 6 hours. This effect was nearly consistent in all treatment groups, including placebo. Therefore it is assumed that the measured mean QTc prolongation is related to surgery and associated anesthetic medications.

Thorough QT Study PALO-03-11

PALO-03-11, a randomized, single dose, double dummy, parallel group, placebo and active comparator (moxifloxacin) controlled design study included five treatments: (1) placebo, (2) I.V. palonosetron 0.25 mg (the market dose for CINV), (3) I.V. palonosetron 0.75 mg, (4) I.V.

palonosetron 2.25 mg, and (5) oral moxifloxacin 400 mg. The high dose of palonosetron evaluated, 2.25 mg, is 9 fold greater than the market dose (0.25mg) for CINV and 30 fold greater than the proposed PONV dose (0.075mg). The study evaluated 221 healthy subjects.

A single dose of 400 mg moxifloxacin increased the QT interval by 11 ms (lower 95% confidence bound 8 ms) 2 hours after dosing, indicating that the study was adequately designed and conducted to detect a mean increase in the QTc of about 5 ms.

No significant effect of palonosetron administration on the QT interval was detected in this thorough QT study. The maximum increase (and corresponding upper two-sided 90% bound) in the placebo-corrected mean change in QTcI from baseline for the 0.25 mg, 0.75 mg and 2.25 mg dose groups were -0.6 ms (3.3 ms), 0.6 ms (5.1 ms) and 1ms (4.8 ms). Similar results were observed for QTcF.

Overall no statistical or experimental evidence was found to demonstrate any potential relationship for corrected QT interval or QT intervals with plasma palonosetron concentrations after single dose administration of intravenous palonosetron including supratherapeutic doses up to 2.25 mg, 9-fold greater than the current marketed 0.25 mg intravenous dose.

The following table showing the frequency for Delta QTc: 30-60 ms, shows that there was no difference between palonosetron and placebo at standard doses.

Table 9: Frequency for Delta QTc: 30~60 ms.

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Treatment A: Placebo	42	1	2.38	1512	1	0.07
Treatment B: Palonosetron 0.25 mg IV	44	0	0.00	1584	0	0.00
Treatment C: Palonosetron 0.75 mg IV	46	1	2.17	1656	1	0.06
Treatment D: Palonosetron 2.25 mg IV	46	5	10.87	1655	7	0.42
Treatment E: Moxifloxacin 400 mg	43	4	9.30	1548	8	0.52

Medical Officer's Comments:

A formal review of PALO-03-11 was done by the CDER Interdisciplinary Review Team for QT studies. Excerpts from that review are included in this Clinical Review, and the full review is available in DFS.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

N/A

7.1.9.3 Standard analyses and explorations of ECG data

N/A

7.1.9.3.1 *Analyses focused on measures of central tendency*

The mean as corrected QT intervals at baseline (Visit 1) were in a range of 378.0 msec (palonosetron 0.075 mg) to 384.1 msec (placebo); QTc by Bazett ranged from 409.9 msec (placebo) to 412.6 msec (palonosetron 0.025 mg); and QTc by Fridericia from 399.6 msec (palonosetron 0.075 mg) to 402.3 msec (palonosetron 0.025 mg).

Mean QT intervals at baseline were similar between all treatment groups and comparable to QT intervals in an averaged healthy population. The slightly higher corrected mean QT intervals are related to an average heart rate >60 beats per minute among all patients in all treatment groups. Mean QTc intervals by Bazett and Fridericia at 15 minutes post-dose increased in each treatment group compared to baseline.

The QTc by Bazett prolongation was consistent throughout all treatment groups with the highest mean increase of 27.0 msec in the placebo group, and lower mean increases of 21.6 msec, 20.3 msec and 23.4 msec in the palonosetron 0.025 mg, 0.050 mg and 0.075 mg groups, respectively.

A similar trend of QT prolongation was also observed for QTc by Fridericia, even though the mean change was smaller, ranging from 12.6 msec (palonosetron 0.050 mg) to 14.6 msec in palonosetron 0.025 mg, 16.2 msec in palonosetron 0.075 mg and 17.8 msec in the placebo group.

Uncorrected QT values showed a small increase in all treatment groups with the exception of the palonosetron 0.050 mg dose group. Changes from baseline were: 1.6 msec, 2.5 msec, -1.5 msec, and 3.7 msec for placebo, palonosetron 0.025 mg, palonosetron 0.050 mg and palonosetron 0.075 mg, respectively. Since QT corrections are calculated based on heart rate, the change from baseline in heart rate is of some relevance since some anesthetic drugs change heart rate, though it is anticipated that the QT corrections account for much of this change. A number of factors including concomitant drugs administered perioperatively may have influenced these QTc values.

At 3-6 hours post-dose, the mean QTc intervals remained slightly increased across all groups compared to baseline values, but started to normalize when compared to 15 minute post-dose values. For QTcB the mean prolongation from baseline was highest in the placebo group with 10.5 msec, and lower in the palonosetron 0.025 mg (10.2 msec) and 0.050 mg (10.1 msec) groups. The smallest QTc prolongation of 9.5 msec was found in the palonosetron highest dose group of 0.075 mg. QTcF showed similar results between treatment groups.

7.1.9.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

N/A

7.1.9.3.3 *Marked outliers and dropouts for ECG abnormalities*

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N/A

7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

N/A

7.1.11 Human Carcinogenicity

N/A

7.1.12 Special Safety Studies

As discussed in 7.1.9.1 of this sNDA review, the sponsor submitted thorough QT study PALO-03-11. A full analysis of this study is contained in section 7.1.9.1, as well as in a separate consult review by the Interdisciplinary QT Review team.

Medical Officer's Comments:

This study was submitted as a major amendment to a previous efficacy supplement in order to address concerns of QT prolongation.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Palonosetron is a highly selective serotonin (5-HT₃) receptor antagonist. Drugs in this pharmacological class are not designated as controlled substances and therefore palonosetron is not considered to have potential for abuse.

7.1.14 Human Reproduction and Pregnancy Data

N/A

7.1.15 Assessment of Effect on Growth

N/A

7.1.16 Overdose Experience

N/A

7.1.17 Post marketing Experience

Post-marketing surveillance, with a dose 3 fold higher (0.25 mg) than proposed for PONV, does not indicate any previously unknown or new events which would require a change in product labeling.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

In pivotal study PALO-04-06, 574 patients were randomized, and 547 (95.3%) received study medication. Overall, in 4 clinical trials, 1952 patients were exposed to palonosetron and placebo. Of the palonosetron-treated subjects, 1232 (81.1 %) received I.V. palonosetron in the Phase 2/3 efficacy trials. The following Table 13 which includes study PALO-04-06 provides information on exposure.

Table 13 (b)
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		Palonosetron	Placebo	Total
Phase 3	I.V.	915	305	1220
Phase 2/3	I.V. ^a	1232	369	1601
Phase 2 ^b	I.V.	317	64	381
	Oral	288	63	351
Overall Exposure in PONV (b) (4)		1520	432	1952

a Includes PALO 04-06, PALO-04-07, and Study 2500

b Study 2500 (IV) and Study 2502 (PO)

7.2.1.1 Study type and design/patient enumeration

Table 8.1.1:1 “Tabular Presentation of Studies: Phase 2 PONV Clinical Studies”, and Table 8.1.1:2 “Tabular Presentation of Studies : Phase 3 PONV Clinical Studies” provide brief descriptive information for all individual studies, including study design, dosing schedule , study location, treatment groups and doses, and patient population. A listing of these tables is contained as an appendix to this document.

7.2.1.2 Demographics

Overall demographic information for Phase 2 and 3 studies are provided below in sponsor’s Table 8.9.4.1.

Table 8.9.4:1 Demographics and Baseline Characteristics in All Phase 2 and Phase 3 Studies¹

Demographic Parameter	Palonosetron ²						Placebo							
	<0.025 mg (n=47)		0.025 mg (n=412)		0.050 mg (n=341)		0.075 mg (n=370)		>0.075 mg (n=350)		Total (n=1520)		Placebo (n=432)	
	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Age (yrs)														
Mean	42.5		43.0		42.3		44.6		40.9		42.9		43.5	
SD	7.6		11.7		11.3		12.1		11.1		11.6		12.4	
Median	42.0		42.0		43.0		44.0		39.0		42.0		42.0	
Range	29-61		18-80		20-86		21-86		19-80		18-86		18-82	
Age Groups (yrs)														
18-39	15	(32)	168	(41)	139	41	137	37	177	51	636	42	172	40
40-64	32	(68)	222	(54)	183	(54)	210	57	164	47	811	53	233	(54)
> 64	0	(0)	22	(5)	19	6	23	(6)	9	3	73	5	27	6
Gender														
Male	0	0	10	2	7	2	12	3	20	6	49	3	17	4
Female	47	100	402	98	334	98	358	97	330	94	1471	97	415	96
Race														
White	25	53	325	79	296	87	298	81	231	66	1175	77	347	80
Black	17	36	54	13	16	5	37	10	76	22	200	13	44	10
Hispanic	4	9	26	6	24	7	30	8	37	11	121	8	35	8
Asian	1	2	5	1	3	1	3	1	4	1	16	1	5	1
Other	0	0	2	0	2	1	2	1	2	1	8	1	1	0

¹ Oral Phase 2 Study 2507; IV Phase 2 Study 2506; IV Phase 3 Studies PALO-04-66 & PALO-04-67
² Doses from weight-based trials are grouped with the fixed dose category closest to the total dose administered
Source: ISS End-of-Trial Table D.1.

Medical Officer's Comments:

As Table 8.9.4:1 shows, in phase 2 and 3 studies submitted with this application only 5% of patients were over 64 years of age. Ninety-seven percent of patients were female and 77% white. The percentage of adverse events in the geriatric population was about the same (71%) as that seen in the 40 to 64 year old group (72%). Within AE categories there was a slight increase in the >64 year age group in the cardiovascular/vascular, infection, and investigational categories (sponsor's Table 8.9.11:2). The sponsor notes that "the numbers of subjects in the oldest group of patients only represents 5% or 6% of subjects overall and individual events can have a large impact on incidence for this group. Cardiac and Gastrointestinal adverse events in the older population were primarily related to bradycardia, constipation and flatulence. The differences between age groups may be due to concurrent diseases in the older population or to increased risk in the older population for post-surgical complications including cardiac events, infections, bleeding, etc. "The medical reviewer agrees with these observations.

7.2.1.3 Extent of exposure (dose/duration)

A total of 1520 subjects were exposed to palonosetron in all Phase 2/3 PONV trials. The following Table 14 summarizes exposure in clinical trials according to palonosetron dose level.

Table 14
Exposure to Palonosetron in Phase 2/3 PONV trials

	Palonosetron (mg)					Total	Placebo	Total
	<0.025	0.025	0.050	0.075	>0.075			
Phase 2	47	108	34	66	350	605	127	732
Phase 3	0	304	307	304	0	915	305	1220
Total Phase 2/3 I.V.	47	374	326	336	149	1232	369	1601
Total all Phase 2/3	47	412	341	370	350	1520	432	1952

Doses <0.025 mg represent the 0.1µg/kg dose level and >0.075 mg represent 3 and 30 µg/kg dose levels from Phase 2 trials.

Medical Officer's Comment:

As the above table shows, exposure at the 0.075 mg dose, the dose proposed for single dosing to prevent PONV (b) (4) was adequate to characterize the safety profile of the drug.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Because palonosetron is currently approved for CINV, additional clinical data is derived from the original NDA, as well as post-marketing information.

7.2.2.1 Other studies

N/A

7.2.2.2 Post-marketing experience

Palonosetron periodic post-marketing safety reviews have not identified any new adverse reactions of concern or new safety signals related to palonosetron administration. There has been no change in the benefit-risk profile of palonosetron since its original approval by FDA. Palonosetron has not been withdrawn and marketing of this drug has not been restricted by any regulatory agency world-wide for safety reasons since palonosetron was first approved by FDA in 2003.

A recent search of the AERS (Adverse Event and Reporting System) by the CDER/OSE (Office of Safety and Epidemiology) reveals the following:

- **Hypersensitivity reactions** – 5 cases
- **Dizziness** – 1 case
- **Tachycardia** – 1 case
- **Constipation** – 1 case
- **Death** – 1 case in a patient with peritoneal carcinoma and sepsis
- **Syncope** – 1 case of a 70-year-old female with advanced ovarian cancer experienced vasovagal syncope during I.V. infusion of Taxotere and after having received palonosetron (0.25 mg I.V. push) and dexamethasone as pre-medications. Taxotere was stopped and the patient transferred to the ER; the event eventually subsided and the patient left the ER on the same day. No other relevant information was provided. Vasovagal syncope is unlabeled in palonosetron USPI and CCSI. Syncope and vasovagal reactions have been reported with Taxotere. A definite drug-event causal association between palonosetron and the reported reaction cannot be established (unassessable). The Company will continue to monitor for the occurrence of syncope with palonosetron.
- **Cardiac events** – 2 cases; A 60-year-old female patient with advanced ovarian cancer, chronic diarrhea, hypertension and renal insufficiency experienced a cardiac arrest after receiving palonosetron (0.25 mg I.V. push) and during I.V. infusion of cimetidine and dexamethasone as pre-medication for a scheduled cycle of chemotherapy. The patient, resuscitated and transferred to the ICU, was also found to have hypomagnesemia and hypocalcemia. Forty-two days later the patient underwent the same preparatory treatment to chemotherapy (palonosetron, cimetidine and dexamethasone) and five minutes into the

I.V. infusion of cimetidine and dexamethasone a second cardiac arrest occurred, preceded by cutaneous signs/symptoms (flushing and pruritus) and high blood pressure. The patient recovered from this second event. The reporting nurse indicated that both events could be considered hypersensitivity reactions, however too many factors involved preclude any definitive assessment. The medical oncologist consulted after the second episode of cardiac arrest indicated that the patient had a history of cardiac arrest secondary to hypoxic encephalopathy, respiratory failure and acute renal failure, and noted that palonosetron-induced QTc interval disturbance in the setting of hypomagnesemia and - possibly - pre-existing cardiac pathologic conditions could explain the observed cardiac events. The Company agrees on the possibility that the therapy given to this patient could have triggered the two episodes of cardiac arrests in a patient with pre-existing cardiac pathologic conditions and hypomagnesemia. QTc prolongation is labeled in palonosetron USPI and CCSI. However, cimetidine is also known to produce cardiac depression and arrhythmias. Therefore, a definite drug-event causal association with palonosetron cannot be clearly established. Follow-up information on the second episode of cardiac arrest (b) (6) could not provide a definite confirmation of the time elapsed between the occurrence of the supposed cardiac arrest and patient's resuscitation without any sequelae. Given the alternative possibility of this event being a respiratory arrest, confirmed by the reporter, the event "respiratory arrest" was added. The Company assessment of drug-event causal association provided in the previous case comment remains unchanged.

A second cardiac event was reported in a 65 year-old female 2 days after receiving Aloxi and dexamethasone prior to receiving study therapy for a pancreatic neuroendocrine tumor. The patient complained of increased abdominal pain as well as high back/chest pain and shortness of breath. The patient's abdominal pain became worse and she was vomiting, therefore she went to the emergency department where she was admitted to the intensive care unit (ICU). She apparently had a clot in her aorta, which was to be treated with surgery. The investigator assessed the causality of the events as probably related to bevacizumab. The causality of oxaliplatin was unknown. The described symptoms (abdominal pain, high back/chest pain, vomiting and shortness of breath) seem related to an aortic thrombosis. Considering the scanty information reported, the Company evaluates palonosetron administration as unlikely related to the reported events.

Medical Officer's Comments:

None of these events are definitive. Surveillance by the FDA Safety Reviewer and Medical Officer is ongoing.

7.2.2.3 Literature

The sponsor has provided an extensive list of published references dealing with PONV (b) (4)
(b) (4)

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-
-
-

(b) (4)

(b) (4)

7.2.3 Adequacy of Overall Clinical Experience

Use of palonosetron for the prevention of PONV (b) (4) is limited to one time dosing/exposure, at the time of surgery. Because the drug is not intended for chronic or long-term use, ICH Guidelines related to extent and duration of exposure for chronically administered drugs do not apply.

Medical Officer's Comment:

The overall exposure to palonosetron in phase 2 and 3 studies was 1520, providing adequate data to evaluate for safety and efficacy of the drug for PONV (b) (4) prevention.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

N/A

7.2.5 Adequacy of Routine Clinical Testing

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Adequacy of metabolic, clearance, and interaction workup is not required for this submission since I.V. Aloxi is currently approved for CINV. Hence these assessments are part of the original drug review.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Because of issues related to QTc prolongation in this drug class, the sponsor conducted an E14 compliant thorough QTc study (PALO-03-11) in 221 healthy male and female subjects. This study is further discussed in section 7.1.9.1 of this review. No additional studies are recommended at this time.

7.2.8 Assessment of Quality and Completeness of Data

Overall data submitted for the safety review of palonosetron is adequate. In addition to a large database from the original CINV trials, and s post-marketing data, information on 1520 patients taking palonosetron and 432 patients taking placebo is provided. One-time administration of the drug, in a monitored setting, provides adequate information.

7.2.9 Additional Submissions, Including Safety Update

N/A

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The incidence of adverse events in all Phase 2 and 3 trials was low overall. The most common adverse events were constipation and headache. These adverse events were seen in the CINV trials as well. A further discussion of drug-related adverse events is contained in section 7.1.5.3.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

In order to provide a comprehensive overview of safety from all PONV (b) (4) subjects receiving palonosetron or placebo, data from the 4 Phase 2–3 clinical trials were pooled and analyzed (n = 1952). Analyses included enumeration; exposure; discontinuations; demography; adverse events (including serious adverse events and adverse events leading to discontinuation); laboratory parameters; vital signs; drug-drug, drug-disease, and drug-demographic interactions; pregnancy, and overdose.

7.4.1.2 Combining data

N/A

7.4.2 Explorations for Predictive Factors

N/A

7.4.2.1 Explorations for dose dependency for adverse findings

N/A

7.4.2.2 Explorations for time dependency for adverse findings

N/A

7.4.2.3 Explorations for drug-demographic interactions

N/A

7.4.2.4 Explorations for drug-disease interactions

N/A

7.4.2.5 Explorations for drug-drug interactions

N/A

7.4.3 Causality Determination

N/A

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The DOSAGE AND ADMINISTRATION section of the proposed label describes the following:

(b) (4)

Choice of the 0.075 mg dose was based on demonstration of superiority over placebo for CR, with a p-Value of 0.0166.

The label does not recommend dose adjustment or special monitoring in geriatric, renal impaired, or hepatic impaired patients.

Medical Officer's Comments:

The selection of a 0.075 mg palonosetron dose is supported by efficacy data from PALO-04-06 and PALO-04-07. This dose is approximately 2/3 of the approved dose for CINV.

8.2 Drug-Drug Interactions

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. In vitro studies indicated that palonosetron is

not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low.

The co-administration of 0.25 mg IV palonosetron and 20 mg I.V. dexamethasone in healthy subjects was safe and well tolerated. In this study there were no pharmacokinetic drug-interactions between palonosetron and dexamethasone.

In an interaction study palonosetron 0.25 mg administered as an I.V. bolus alone or co-administered with aprepitant to healthy subjects.

Aprepitant did not affect the AUC_{0-∞} of palonosetron but did increase its C_{max} by 15% with the 90% CI of bioequivalence comparison being 61.8%-157%, which is outside the bioequivalence acceptance criteria of 80% to 125%. The adverse events observed in both treatments were similar. The BioPharm reviewer agrees to the sponsor's conclusion that co-administration of aprepitant with palonosetron is tolerable. Based on the C_{max} observed in Study 2500 at the dose of 30 µg and the highest dose studied clinically, 2.5 mg, there is no safety concern over the 15% increase of C_{max} by aprepitant.

A study in healthy volunteers involving single-dose IV palonosetron (0.75 mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

In controlled clinical trials, ALOXI injection has been safely administered with corticosteroids, analgesics, antiemetics/antinauseants, antispasmodics and anticholinergic agents.

Medical Officer's Comments:

As noted previously in this review, interactions with aprepitant may not be pertinent to the PONV, (b) (4) indication since the drugs will not be co-administered for these indications.

8.3 Special Populations

Across all studies submitted for this NDDA (study 2500, PALO-04-06, PALO-04-07) only 6% of patients were >64 years of age, compared with 40% between the ages of 18 and 39, and 54% between the ages of 40 and 64. Therefore minimal safety or efficacy information was obtained for this age demographic.

8.4 Pediatrics

N/A

8.5 Advisory Committee Meeting

N/A

8.6 Literature Review

N/A

8.7 Post marketing Risk Management Plan

N/A

8.8 Other Relevant Materials

9 OVERALL ASSESSMENT

9.1 Conclusions

In this PONV (b) (4) submission a smaller dose of palonosetron than that currently approved for CINV was studied. Administration was on a one time basis, prior to the induction of anesthesia.

Adverse events were minimal, and comparable to those attributed to the medication in CINV trials. A thorough QT study was submitted by the sponsor in order to further characterize the effect of palonosetron on the QT interval. At doses as high as 2.25 mg, no significant effect on QT was seen.

Efficacy was seen in the first 24 hours, and the cumulative 0 to 48 and 0 to 72 hour time periods, but was lacking from 24 to 72 hours.

9.2 Recommendation on Regulatory Action

The sponsor has submitted a bundled application with three components:

- Prevention of PONV for up to three days after surgery
- (b) (4)
- Removal of QT warning information from the label

It is recommended that palonosetron be approved to prevent nausea and vomiting after surgery for the first 24 hours. (b) (4) These recommendations are based on clinical studies PALO-04-06, Study 2500, and to a lesser extent PALO-04-07.

It is also recommended that some of the sponsor's proposed labeling revisions, such as removing QT prolongation warnings be approved. The following is recommended by the QT interdisciplinary review (QT-IRT) team. The Medical Officer Reviewer agrees with these recommendations.

The QT-IRT suggests that the sponsor's proposed label be changed so that the final sentence states "The study demonstrated no *significant* effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg." Aloxi® has an effect on the QT interval but it is small.

Additionally, the QT-IRT recommends that the statement in the current label "In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration" be retained.

9.3 Recommendation on Post marketing Actions

N/A

9.3.1 Risk Management Activity

N/A

9.3.2 Required Phase 4 Commitments

N/A

9.3.3 Other Phase 4 Requests

N/A

9.4 Labeling Review

To be addressed in a separate document.

10 APPENDICES

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

Labeling review will be contained in separate document.

Clinical Review
Nancy F. Snow
NDA 21-372/S-008
Palonosetron, Aloxi®

REFERENCES

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

/s/

Nancy Snow
2/15/2008 12:20:52 PM
MEDICAL OFFICER

Hugo Gallo Torres
2/15/2008 03:25:18 PM
MEDICAL OFFICER

MTL agrees with MOR's recommendations/conclusions: 1. PONV

a) Efficacy shown for 0 to 24h (b)(4)
(b)(4) (4)

(b) (4)

Removal of QT Warning; and 3. No additional
safety concerns that would preclude an APPROVAL Regulatory
Action.